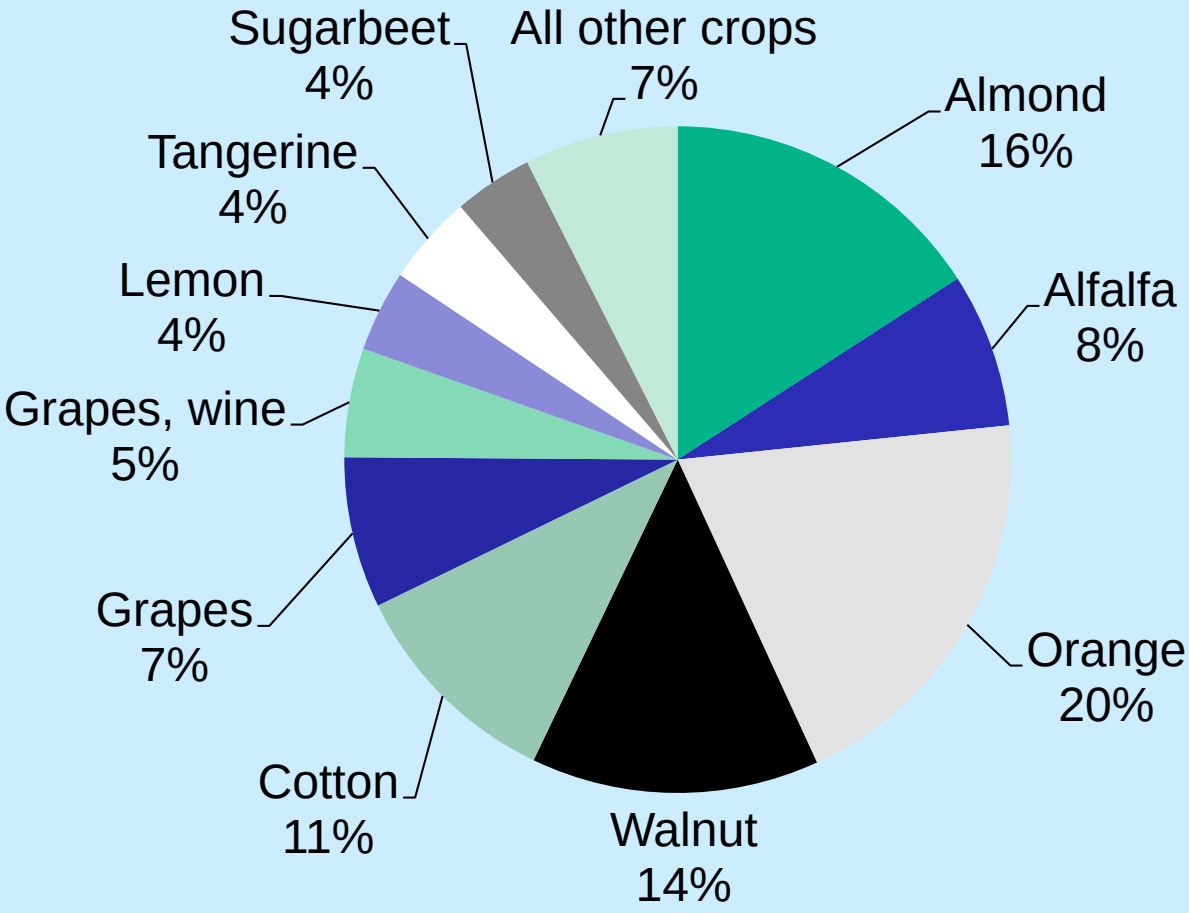
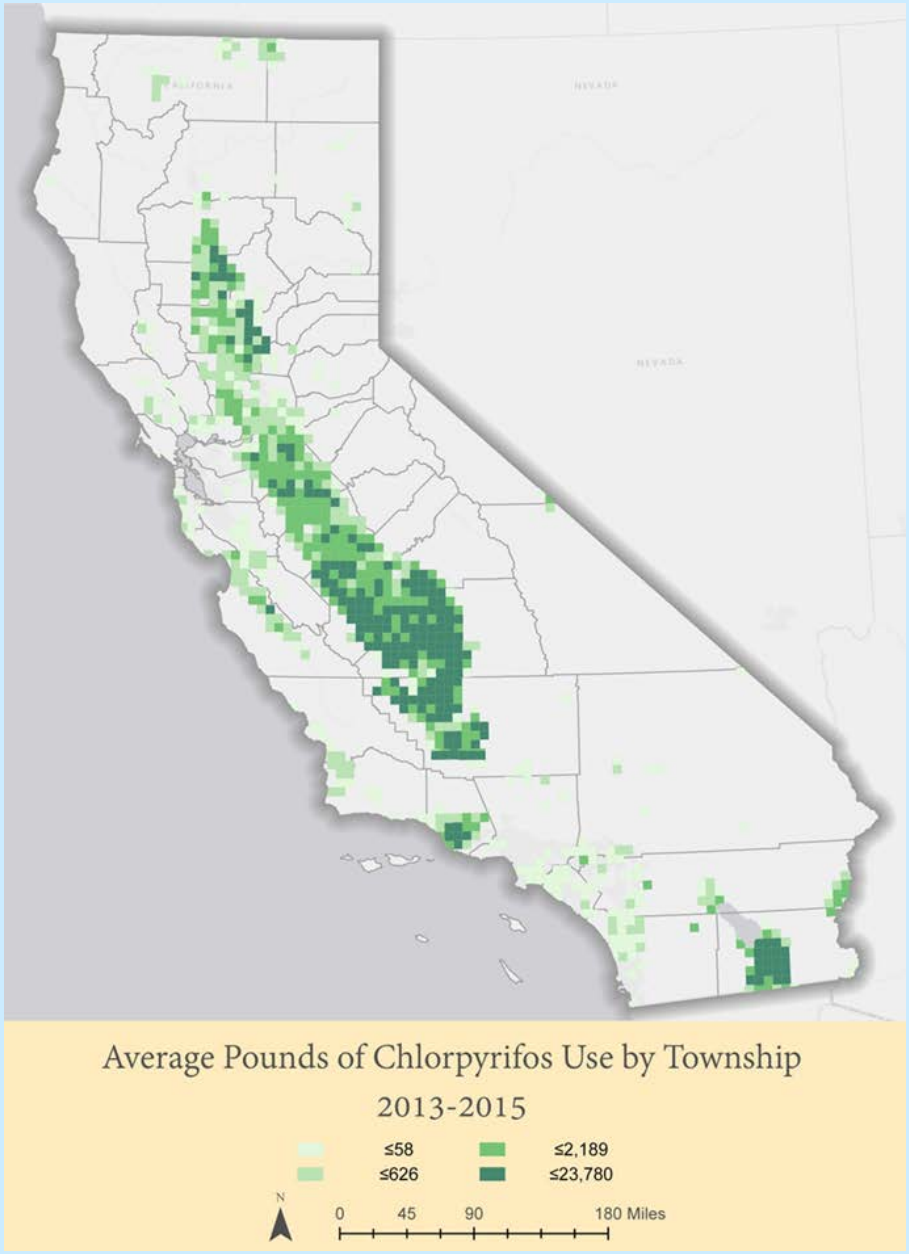
Chlorpyrifos use

- Chlorpyrifos is an organophosphate insecticide used on more than 60 crops



Chlorpyrifos use by township (6x6 mile area)

- Most use occurs in the Central Valley, Central Coast, and Imperial regions



California Toxic Air Contaminant Act
Food and Agricultural Code sections 14021-14027

- Air Resources Board (ARB) is required to monitor pesticides at DPR's request
- DPR is required to assess bystander health risks from pesticide air exposure
  - Scientific Review Panel (SRP) reviews DPR assessment
  - California Code of Regulations specifies the criteria to list a pesticide as a toxic air contaminant (TAC)
- DPR is required to mitigate bystander health risks from pesticide air exposure

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: November 3, 2016

SUBJECT: Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review

PC Code: 059101
Decision No.: 522687
Petition No.: NA
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D436317
Registration No.: NA
Regulatory Action: Registration Review
Case No.: NA
CAS No.: 2921-88-2
40 CFR: 40 CFR§180.342

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And

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TO: Dana Friedman, Chemical Review Manager
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1.0 Executive Summary

This document presents the revised human health risk assessment for the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Registration Review of the organophosphate (OP) insecticide chlorpyrifos.

Background
A preliminary human health risk assessment (HHRA) for chlorpyrifos was completed on June 30, 2011 (D. Drew *et. al*, D388070, 06/30/2011) as part of the FIFRA Section 3(g) Registration Review program. A revised HHRA was completed in 2014 (D. Drew *et. al*, D424485, 12/29/2014) to address comments received on the preliminary HHRA and to incorporate new information and new approaches that had become available since the June 2011 risk assessment. Most notably, the 2014 revised HHRA incorporated the following: (1) a physiologically-based pharmacokinetic-pharmacodynamic (PBPK-PD) model for deriving toxicological points of departure (PoDs) based on 10% red blood cell (RBC) acetyl cholinesterase (AChE) inhibition; and (2) evidence on neurodevelopmental effects in fetuses and children resulting from chlorpyrifos exposure as reported in epidemiological studies, particularly the results from the Columbia Center for Children's Environmental Health (CCCEH) study on pregnant women which reported an association between fetal cord blood levels of chlorpyrifos and neurodevelopmental outcomes. The 2014 revised HHRA retained the 10X Food Quality Protection Act (FQPA) Safety Factor (SF) because of the uncertainties that neurodevelopmental effects may be occurring at doses lower than those that cause 10% RBC AChE inhibition and used for the PoD.

Based on the aggregate risks identified in 2014 (D. Drew *et. al*, D424485, 12/29/2014), a proposed rule (PR) for revoking all tolerances of chlorpyrifos was published in the Federal Register on November 6, 2015 (80 FR 69079). At that time, the EPA had not completed a refined drinking water assessment or additional analysis of the hazard from chlorpyrifos that was suggested by several commenters to the EPA's 2014 registration review revised HHRA. Those commenters raised the concern that the use of 10% RBC AChE inhibition for deriving PoDs for chlorpyrifos may not provide a sufficiently health protective human health risk assessment given the potential for neurodevelopmental outcomes. Accordingly, following the issuance of the proposed rule, the EPA conducted additional hazard analyses using data on chlorpyrifos levels in fetal cord blood (reported by the CCCEH study investigators) as the source for new PoDs for risk assessment.

The EPA consulted the FIFRA Scientific Advisory Panel (SAP) for scientific advice on the proposed approach of using the CCCEH cord blood data at a meeting on April 19 – 21, 2016. The 2016 SAP did not support using the cord blood data quantitatively for deriving PoDs. However, the Panel concluded that epidemiology and toxicology studies suggest there is evidence for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% RBC AChE inhibition, which was used as the PoD in the EPA's 2014 RHHRA and for the 2015 proposed revocation rule. The SAP therefore appears to have rejected both the approach the EPA put forward in its proposed rule derived from the 2014 risk assessment as well as the EPA's initial efforts to address the results of the CCCEH study quantitatively.

The SAP report, however, did present the EPA with a path forward for a third approach to setting the PoDs. First, as a foundation, it is important to note that the SAP was supportive of the EPA's use of the PBPK model as a tool for assessing internal dosimetry from typical Office of Pesticide Programs (OPP) exposure scenarios using peer reviewed exposure assessment approaches (e.g., food, water, residential, occupational). Use of the PBPK model coupled with typical exposure scenarios provides the strongest scientific foundation for chlorpyrifos human health risk assessment and is the approach used in this 2016 assessment. Given that the window(s) of susceptibility are currently not known for the observed neurodevelopmental effects, and the uncertainties associated with quantitatively interpreting the CCCEH cord blood data, the SAP recommended that the agency use a time weighted average (TWA) blood concentration of chlorpyrifos for the CCCEH study cohort as the PoD for risk assessment. The EPA has chosen to follow that advice in this assessment. Thus, for this assessment, the PBPK model was used to determine the TWA blood level expected from post-application exposures from the chlorpyrifos indoor crack and crevice use scenario. This scenario was selected as it represents the most appropriate exposure for the women in the CCCEH cohort (i.e., crack and crevice was the predominant application type during the time of the CCCEH study and is considered protective of other possible exposures for the women in the cohort). In order to derive a TWA of chlorpyrifos concentrations in blood for a predicted risk assessment endpoint, the dose reconstruction analysis assumed exposures for 2 hours per day with a daily shower, for a total of 30 days. Additionally, chlorpyrifos residues were assumed to dissipate 10% daily; that is, the total amount of residue available for transfer from the treated floor is assumed to reduce by 10% for each subsequent day of exposure until the end of the 30th day prior to the next application.

The TWA blood level was used as the internal dose for determining separate PoDs for infants, children, and adults exposed to chlorpyrifos. These separate PoDs have been calculated by PBPK modeling for dietary (food, drinking water), residential, and occupational exposures. With the exception of the acute (single day) exposure assessment for non-occupational bystander post-application inhalation exposures, only steady state[1] (repeat) exposure durations are considered in this assessment as assessing the steady state exposure duration most closely matches the TWAs calculated for the PoDs. The PoDs derived from the TWA blood level are protective of any additional acute exposures to chlorpyrifos.

The TWA blood level resulting from chlorpyrifos exposure from the crack and crevice scenario is considered a lowest-observed-adverse-effect-level (LOAEL) rather than a no-observed-adverse-effect-level (NOAEL), since this is the exposure level likely to be associated with neurodevelopmental effects reported in the CCCEH study. In situations where the agency selects a PoD from a study where a NOAEL has not been identified, the EPA generally will retain the FQPA SF of 10X to account for the uncertainty in using a LOAEL. Therefore, the 10X FQPA SF has been retained in this revised risk assessment for chlorpyrifos. The revised risk assessment also applies a 10X uncertainty factor for intraspecies variability because of the lack

[1] Organophosphates (OPs), including chlorpyrifos, exhibit a phenomenon known as steady state AChE inhibition. After repeated dosing at the same level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChEI at a given dose remains relatively consistent across duration. In general, OPs reach steady state within 2-3 weeks. Therefore, for OPs it is appropriate to assess steady state exposure durations (up to 21 days) instead of longer term exposures. The steady state point of departure is protective of any longer exposure duration, including chronic exposure.

of sufficient information to reduce or remove this factor. Typically, the agency uses animal studies for selection of PoDs and, as such, retains a 10X interspecies factor for extrapolation of the animal data to assess human health. However, with use of the PBPK-PD model which accounts for the pharmacokinetic and pharmacodynamic differences between animals and humans to derive PoDs, it is appropriate to reduce the interspecies factor to 1X. Therefore, the total uncertainty factor for chlorpyrifos in this 2016 risk assessment is 100X.

For the dietary assessment, PoDs are divided by the total uncertainty factor (100) to derive a population adjusted dose (PAD). The chlorpyrifos exposure values resulting from dietary modeling are compared to the PAD. There are potential risks of concern when estimated dietary risk exceeds 100% of the PAD.

For the residential and occupational assessments, margins of exposure (MOEs) are calculated by comparing the PoDs to the calculated exposures for each scenario. The resulting MOEs are then compared to the level of concern (LOC) of 100 (the total uncertainty factor is the LOC). If calculated MOEs are less than 100 then a risk of concern is identified for that exposure scenario.

This 2016 human health risk assessment only provides limited summary information and substantially relies on the following previous documents developed for chlorpyrifos, and the updated drink water assessment, which contain more detailed evaluations of the risk assessment approach, scientific literature, and the PBPK model:

- D. Drew *et al.*, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review, December 29, 2014, D424485;
- U.S. Environmental Protection Agency, Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides, September 15, 2015, D331251;
- R. Bohaty and J. Hetrick. Chlorpyrifos Registration Review Drinking Water Assessment, April 14, 2016, D432921
- U.S. Environmental Protection Agency, Chlorpyrifos Issue Paper: Evaluation of Biomonitoring Data from Epidemiology Studies, March 11, 2016 and supporting analyses presented to the FIFRA Scientific Advisory Panel's (SAP) meeting on April 19-21, 2016, (EPA-HQ-OPP-2016-0062).

Use Profile

Chlorpyrifos is a broad-spectrum, chlorinated OP insecticide. Registered use sites include a large variety of food crops, and non-food use settings. Public health uses include aerial and ground-based fogger adulticide treatments to control mosquitoes. There is a wide range of registered formulations, application rates, and application methods. Registered labels generally require that handlers use normal work clothing (i.e., long sleeved shirt and pants, shoes and socks) and coveralls, chemical resistant gloves, and dust/mist respirators. Also, some products are marketed in engineering controls such as water soluble packets. The restricted entry intervals (REIs) on the registered chlorpyrifos labels range from 24 hours to 5 days. The pre-harvest intervals (PHIs) range from 0 days (Christmas trees) to 365 days (ginseng).

Dietary Risk Assessment

This assessment indicates that steady state dietary exposure analysis is highly refined. The large

majority of food residues used were based upon U. S. Department of Agriculture's Pesticide Data Program (PDP) monitoring data. Percent crop treated information and food processing factors were included, where available. All commodities with U.S. tolerances for residues of chlorpyrifos are included in the assessment.

The steady state dietary (food only) exposures for chlorpyrifos are of risk concern (> 100% steady state PAD for food ($ssPAD_{food}$)) at the 99.9^{th} percentile of exposure for all population subgroups analyzed. Children (1-2 years old) is the population subgroup with the highest risk estimate at 14,000% of the $ssPAD_{food}$.

For chlorpyrifos, a drinking water level of comparison (DWLOC) approach is used to calculate the amount of exposure available in the dietary 'risk cup' for chlorpyrifos in drinking water after accounting for chloropyrifos exposure from food. This DWLOC is then compared to the estimated drinking water concentration (EDWC) to determine if there is a risk of concern for drinking water exposures. However, because this assessment indicates that dietary risks from food alone are of concern it is not possible to calculate a DWLOC; essentially the steady state DWLOC is '0' after accounting for food exposures.

Hypothetically, if there were no exposure to chlorpyrifos from food and the entire dietary 'risk cup' was available for drinking water, the resulting steady state DWLOC for infants (the most highly exposed population subgroup for water) would be 0.014 ppb. An EDWC at or exceeding this concentration would be considered a risk of concern for exposures to chlorpyrifos in drinking water. The refined chlorpyrifos EDWCs are presented in the revised drinking water assessment (DWA) (Bohaty, R., 4/14/2016, D432921, Chlorpyrifos Revised Drinking Water Assessment for Registration Review).

Residential (Non-occupational) Risk Assessment
Residential post-application exposures can occur for adults and children golfing on chlorpyrifos-treated courses. The residential post-application assessment considered and incorporated all relevant populations and chemical-specific turf transferable residue (TTR) data. This assessment indicates that all residential post-application exposures are of concern (i.e., MOEs are < 100) on the day of application (Day 0); all MOEs < 1 (LOC = 100). Further, all residential post-application exposure scenarios assessed following aerial and ground Ultra Low Volume (ULV) mosquitocide applications result in risks of concern; MOEs ranged from < 1 to 68 (LOC = 100).

Non-Occupational Spray Drift Exposure and Risk Assessment
A quantitative non-occupational spray drift (from treatment of agricultural fields) assessment was conducted for this assessment. Adult dermal and children's (1 < 2 year old) dermal and incidental oral risk estimates from indirect exposure to chlorpyrifos from spray drift result in risk estimates of concern at the field edge. All scenarios require buffer distances of > 300 feet to be below the level of concern.

Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Assessment
In the 2014 risk assessment, the agency did not include a quantitative assessment of post-application inhalation exposure to bystanders. This assessment was not included since two vapor-phase AChE inhibition inhalation toxicity studies were submitted and reviewed which

demonstrated that no inhibition of AChE occurred even at the saturation concentration. Therefore, it was assumed that there were no anticipated risks of concern from exposure to the volatilization of either chlorpyrifos or chlorpyrifos oxon. However, in the current assessment, the points of departure for risk assessment have been chosen to be protective of potential neurological effects that occur below levels where AChE inhibition could occur. For that reason, a quantitative bystander/volatilization assessment has been included in this update.

The EPA has assessed residential bystander exposure from field volatilization of applied chlorpyrifos based on available *ambient* (five studies/11 locations) and *application site* (one study/2 locations) air monitoring data. Of the 11 acute *ambient* air concentrations assessed, six resulted in risk estimates that are of concern (i.e., MOEs < 100). Only one steady-state *ambient* air concentration resulted in a risk estimate not of concern (i.e., MOEs > 100). For the *application site* air concentrations assessed, all resulted in risk estimates of concern (i.e., MOEs < 100).

Aggregate Risk Assessment
For the chlorpyrifos aggregate assessment, the EPA has traditionally used a DWLOC approach to calculate the amount of exposure available in the total 'risk cup' for chlorpyrifos in drinking water after accounting for any chloropyrifos exposures from food and residential use. This DWLOC is then compared to the EDWC to determine if there is an aggregate risk of concern. However, because the dietary risks from food exposure alone and from residential exposure alone are of concern, it is not possible to calculate a DWLOC; essentially, the steady state aggregate DWLOC is '0' after accounting for food and residential exposures. Quantitatively aggregating (combining) residential, food, and drinking water exposures would result in risks of concern.

Occupational Risk Assessment
Steady state occupational handler and post-application exposure analyses were previously completed for the registered uses of chlorpyrifos. However, occupational exposures and risk estimates have been updated to incorporate the revised PBPK-derived PoDs. The scenarios, assumptions, and exposure inputs have not changed since the previous assessment.

Using the updated PBPK-derived steady state PoDs and uncertainty factors (dermal and inhalation LOC = 100), all agricultural occupational handler scenarios, all primary seed treatment handler scenarios, and all secondary seed treatment (planter) scenarios are of concern with label-specified and maximum levels of personal protective equipment (PPE) or engineering controls (MOEs < 100).

Using the updated PBPK-derived steady state PoDs and uncertainty factors (dermal LOC = 100), all occupational dermal post-application scenarios were of concern on Day 0. The REIs on the registered chlorpyrifos labels range from 24 hours to 5 days. On average, scenarios were not of concern $\geq$ 18 days after treatment.

2.0 Use Profile

Chlorpyrifos (0,0-diethyl-0-3,5,6-trichloro -2-pyridyl phosphorothioate) is a broad-spectrum,

chlorinated OP insecticide. Registered use sites include a large variety of food crops (including fruit and nut trees, many types of fruits and vegetables, and grain crops), and non-food use settings (e.g., golf course turf, industrial sites, greenhouse and nursery production, sod farms, and wood products). Public health uses include aerial and ground-based fogger adulticide treatments to control mosquitoes. There are also residential uses of roach bait products and ant mound treatments. Permanent tolerances are established (40 CFR§180.342) for the residues of chlorpyrifos in/on a variety of agricultural commodities, including meat, milk, poultry and eggs. There are also tolerances for use in food handling/service establishments (FHE or FSE). Chlorpyrifos is manufactured as granular, microencapsulated liquid, soluble concentrate liquid, water dispersible granular in water soluble packets (WSP), wettable powders in WSPs, impregnated paints, cattle ear tags, insect bait stations and total release foggers. There is a wide range of application rates and methods. The residues of concern for risk assessment purposes are chlorpyrifos and chlorpyrifos oxon under some circumstances.

3.0 Tolerance Considerations

See Section 2.0 and Appendix 8 of D22485 (D. Drew *et al.*, 12/29/2014) for details regarding the analytical enforcement method, U.S. tolerances and international residue levels for chlorpyrifos.

4.0 Chemical Identity and Physical/Chemical Properties

See Sections 3.1 and 3.2 and Appendix 7 of D22485 (D. Drew *et al.*, 12/29/2014) for details regarding the chemical identity and physical/chemical characteristics of chlorpyrifos.

5.0 Hazard Characterization and Dose-Response Assessment

5.1 Introduction & Background

Historically, the EPA has used AChE inhibition as the critical effect for deriving risk assessment PoDs for OP pesticides, including chlorpyrifos. However, there is a breadth of information available on the potential adverse neurodevelopmental effects in infants and children as a result of prenatal exposure to chlorpyrifos. Over the last several years, the agency has taken a stepwise, objective, and transparent approach to evaluate, interpret, and characterize the strengths and uncertainties associated with the available neurodevelopmental information. This effort has involved extensive collaboration across the EPA and also within the Federal government.

The stepwise evaluation began with the September 2008 FIFRA SAP. The SAP evaluated the agency's preliminary review of available literature and research on chlorpyrifos, with a particular focus on effects seen in women and children following chlorpyrifos exposures (USEPA, 2008). Subsequently, the agency has developed approaches for risk assessment of semi-volatile pesticides (USEPA, 2009), and developed the draft "Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment" to better integrate epidemiology data with other types of experimental data in pesticide risk assessments (USEPA, 2010; FIFRA SAP 2010a,b). In early 2011, the FIFRA SAP reviewed the chlorpyrifos physiologically based pharmacokinetic – pharmacodynamic (PBPK-PD) model to conduct quantitative risk assessment.

The model estimates AChE inhibition in humans following exposure to chlorpyrifos and/or the oxon from a variety of exposure pathways (FIFRA SAP 2011).

In 2012, the agency convened another FIFRA SAP to review the latest experimental data related to AChE inhibition, cholinergic and non-cholinergic adverse outcomes, including neurodevelopmental studies on behavior and cognition effects (FIFRA SAP 2012[2]). Similarly, the agency also performed an in-depth analysis of the available chlorpyrifos biomonitoring data and of the available epidemiologic studies from three major children's health cohort studies in the U.S., including those from the Columbia University. The agency also explored plausible hypotheses on mode of actions/adverse outcome pathways (MOAs/AOPs) leading to neurodevelopmental outcomes seen in the biomonitoring and epidemiology studies.

Following the 2012 SAP meeting, the agency solicited additional input from federal experts in the areas of Magnetic Resonance Imaging (MRI) and neurobehavioral testing in children to further clarify results obtained by examination of the epidemiological cohorts.[3] Also, the agency evaluated the potential for chlorpyrifos exposure to lead to the neurobehavioral outcomes seen in the cohorts, and the ability of other environmental exposures to affect the interpretation of the results from the Columbia University studies.

In December, 2014, the agency released "Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review" (herein called "HHRA", D. Drew *et al.*, D424485, 12/29/2014). The 2014 assessment used a PBPK-PD model (Appendix 2) to derive human PoDs based on 10% RBC AChE inhibition; for more information see Appendix 2 of D424485 (D. Drew *et al.*, 12/29/2014). In accordance with the recommendation of the FIFRA SAP (2012), the agency conducted a dose reconstruction analysis based on registered uses available for use in indoor residential areas prior to the year 2000. The highest exposures resulted from the registered broadcast use in residential homes. Based on the output from the PBPK-PD model, for the highest exposure considered (i.e., contact with hard floors following indoor broadcast use of a 1% chlorpyrifos formulation), <10% RBC AChE inhibition in pregnant women and young children would be expected from residential uses. It is noteworthy that all estimates of exposure based on conservative assumptions lead to predicted AChE inhibition levels < 10%. The chlorpyrifos 2014 revised HHRA included retention of the 10X FQPA SF for all populations assessed; including infants, children, youths, and women of childbearing age. The 10X FQPA safety factor was retained based on the conclusion that, given the totality of evidence, chlorpyrifos likely played a role in the neurodevelopmental outcomes reported by the Columbia University investigators but uncertainties, such as the lack of an established MOA/AOP for neurodevelopmental effects and the exposure to multiple AChE-inhibiting pesticides, precluded definitive causal inferences. As a result, there is sufficient uncertainty in the human dose-response relationship for neurodevelopmental effects which prevents the agency from reducing or removing the statutory 10X FQPA SF (D. Drew *et al.*, D424485, 12/29/2014).

In 2013, the EPA sought to obtain the original raw data used to support certain epidemiological analyses of *in* utero exposure to chlorpyrifos and subsequent adverse neurodevelopmental health outcomes in children generated by the CCCEH. While the researchers did not agree to provide

[2] https://www.regulations.gov/docket?D=EPA-HQ-OPP-2012-0040
[3] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170

these data to the EPA, agency staff gained valuable insight into the conduct of the study and the data that were collected in a visit to Columbia University in April 2013. The agency wrote a summary of the 2013 meeting with researchers from Columbia University which can be found in "Appendix 6 Columbia Center for Children's Environmental Health (CCCEH) Epidemiology Data Acquisition "Raw Data Request" of Drew *et. al*, D424485, 12/29/2014. In the summer of 2015, Dr. Dana Barr of Emory University (formerly of CDC) provided the EPA with limited raw urine and blood data in her possession from the three cohorts. However, the files provided from Dr. Barr are not useful for the EPA's current purpose of assessing risk to chlorpyrifos (D. Vogel, Record of Correspondence, 10/2016). The EPA does not have any of the other measurements of the children in the cohort (e.g., chlorpyrifos blood data, interviews, test or IQ scores).

In a 2016 white paper, the agency proposed using data on cord blood reported from the investigators at the Columbia Center for Children's Environmental Health (CCCEH) as the source for new PoDs for risk assessment. This 2016 white paper was reviewed by the FIFRA SAP in April, 2016[4]. The 2016 Panel did not support using the CCCEH chlorpyrifos concentrations in cord blood quantitatively to derive PoDs for risk assessment. The Panel noted a number of uncertainties, including: the use of results from a single longitudinal study without replication from another cohort; the lack of verification and replication of the analytical chemistry results that reported very low levels of chlorpyrifos (pg/g); and the lack of raw data available for independent evaluation. Importantly, however, the Panel agreed that "both epidemiology and toxicology studies suggest there is evidence for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% red blood cell (RBC) acetylcholinesterase (AChE) inhibition (i.e., toxicity at lower doses)." Moreover, the Panel did support the use of the PBPK model to assess internal dosimetry from various exposure scenarios. The SAP specifically stated that PBPK modelling "is a valuable tool to interpret the biomonitoring data in circumstances where multiple routes of exposure occur and when based on best available information as inputs."

Therefore, based on the evidence collected from 2014 to date, as summarized above, the agency has updated its HHRA for the existing uses of chlorpyrifos. This 2016 human health risk assessment provides limited, summary information and substantially relies on previous documents developed for chlorpyrifos which contain more detailed evaluations of scientific literature and the PBPK model:

- D. Drew *et al.*, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review, December 29, 2014, D424485; and
- U.S. Environmental Protection Agency, Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides, September 15, 2015, D331251.

5.2 Summary of the Literature Review on Neurodevelopmental Effects

Detailed summaries of the epidemiological studies used in this literature review can be found either in the 2014 chlorpyrifos HHRA (D. Drew *et al.*, D424485, 12/29/2014), the 2015 literature review for other organophosphates (OPP/USEPA, D331251, 09/15/2015), and reviews of newer studies (E. Holman, D432184, 03/25/2016). Only brief summaries of the literature reviews are

[4] https://www.regulations.gov/docket?D=EPA-HQ-OPP-2016-0062

provided below.

Newer lines of research on OPs have raised some uncertainty about the agency's risk assessment approach of using AChE inhibition for deriving PoDs. These uncertainties are in the areas of potential AOPs; *in vivo* animal studies; and notably results seen in epidemiological studies in mothers and children, with regard to the potential for neurodevelopmental effects in fetuses and children. Many of these studies have been the subject of review by the agency over the last several years as part of the development of the 2014 chlorpyrifos HHRA (D. Drew *et al.*, D424485, 12/29/2014).

A review of the scientific literature on potential MOAs/AOPs[5] leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting (USEPA, 2012) and updated for the December 2014 chlorpyrifos HHRA (D. Drew *et al.*, D424485, 12/29/2014). In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers that include targets other than AChE inhibition, including cholinergic and non-cholinergic systems, signaling pathways, proteins, and others. However, no one pathway has sufficient data to be considered more credible than the others. Published and submitted guideline developmental neurotoxicity (DNT) laboratory animal studies have been reviewed for OPs (D. Drew *et al.*, D424485, 12/29/2014 and USEPA, D331251, 09/15/2015). Neurobehavioral alterations in laboratory animals were often reported; however, at AChE inhibiting doses. Moreover, there was generally a lack of consistency in pattern, timing, and dose-response for these effects; and a number of studies were of low quality. However, the information on neurobehavioral effects as a whole provides evidence of long-lasting neurodevelopmental disorders in rats and mice following gestational exposure to OPs.

Initially, the agency focused on epidemiological studies from three US cohorts: 1) The Mothers and Newborn Study of North Manhattan and South Bronx performed by the CCCEH at Columbia University; 2) the Mt. Sinai Inner-City Toxicants, Child Growth and Development Study or the "Mt. Sinai Child Growth and Development Study;" and 3) the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by researchers at University of California Berkeley. The agency has evaluated these studies and sought external peer review (FIFRA SAP reviews in 2008 and 2012; federal panel, 2013[6]) and concludes they are of high quality. In the three US epidemiology cohort studies, mother-infant pairs were recruited for the purpose of studying the potential health effects of environmental exposures during pregnancy on subsequent child development. Each of these cohorts has evaluated the association between prenatal chlorpyrifos and/or OP exposure with adverse neurodevelopmental outcomes in children through age 7-11 years. For the 2014 chlorpyrifos HHRA (D. Drew *et al.*, D424485, 12/29/2014), the EPA included epidemiologic research results from these three US prospective birth cohort studies but primarily focused on the results of CCCEH since this cohort has published studies on the association between cord blood levels of chlorpyrifos and neurodevelopmental outcomes. The agency retained the FQPA 10X SF in the 2014 chlorpyrifos revised risk assessment, in large part, based on the findings of these studies.

[5] Mode of action (MOA) and adverse outcome pathways (AOPs) describe a set of measureable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events.
[6] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170

In the 2015 updated literature review (USEPA, D331251, 09/15/2015), the agency conducted a systematic review expanding the 2012/2014 review which was focused only on US cohort studies with particular emphasis on chlorpyrifos. The expanded 2015 review includes consideration of the epidemiological data on any OP pesticide, study designs beyond prospective cohort studies, and non-U.S. based studies. The updated literature review identified seven studies which were relevant (Bouchard *et al.,* 2010; Fortenberry *et al.,* 2014; Furlong *et al.,* 2014; Guodong *et al.,* 2012; Oulhote and Bouchard, 2013; Zhang *et al.*, 2014; Shelton *et al.*, 2014). These seven studies have been evaluated in context with studies from the 2012/2014 review (D. Drew *et al.,* D424485, 12/29/2014). In addition, the agency has also reviewed more recent studies from CCCEH (Rauh *et al*., 2015) and a pooled analysis of U.S. cohort studies (Engel *et al*., 2015) (E. Holman, D432184, 03/25/2016). As discussed below, Rauh *et al.* (2015) provides further evidence of neurodevelopmental outcomes in the CCCEH study. The Engel *et al.* (2015) study shows relatively consistent results compared to previous studies conducted at 24 months (Engel *et al.*, 2011; Rauh *et al.*, 2006). Only a brief summary of this review is provided below. The agency continues to conclude that the 3 U.S. cohort studies (CCCEH, CHAMACOS, and Mt. Sinai) provide the most robust available epidemiological evidence.

The agency acknowledges the lack of established MOA/AOP pathway, the inability to make strong causal linkages, and the unknown window(s) of susceptibility. These uncertainties do not undermine or reduce the confidence in the findings of the epidemiology studies. The epidemiology studies reviewed in the 2012/2014 and 2015 literature reviews represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements. Despite differences in study design, with the exception of two negative studies in the 2015 literature review (Guodong *et al.,* 2012; Oulhote and Bouchard, 2013) and the results from the more recent Engel *et al.* (2015) study[7], all other study authors have identified associations with neurodevelopmental outcomes associated with OP exposure; these conclusions were across four cohorts and twelve study citations. Specifically, there is evidence of delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children who were exposed to OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios 2-4 fold increased in some instances), and observed evidence of exposures-response trends in some instances, *e.g.*, intelligence measures.

The CCCEH study primarily tested for the presence of chlorpyrifos in cord blood, and therefore remains the most relevant for the purposes of chlorpyrifos risk assessment. As summarized above, when comparing high to low exposure groups at 3 years of age in the CCCEH study (Rauh *et al.*, 2006), there were increased odds of:

- Mental delay (odds ratio; OR=2.4; 95% Confidence interval (CI): 1.1–5.1);
- Psychomotor delay (OR=4.9; 95% CI: 1.8–13.7);
- Attention disorders (OR=11.26; 95% CI: 1.79–70.99);
- Attention deficit hyperactivity disorder (ADHD) (OR=6.50; 95% CI: 1.09–38.69); and
- Pervasive Developmental Disorders (PDD) (OR=5.39; 95% CI: 1.21–24.11).

In a follow-up study at age 11, CCCEH study authors observed increased odds of mild to

[7] It is noted that the CCCEH study participants included in the Engel et al (2015) study are women enrolled from 2000-2001, i.e. after the cancellation of the residential uses of chlorpyrifos.

moderate tremor when comparing high to low exposure groups (Rauh *et al.*, 2015). Rauh *et al.*, (2011) evaluated relationship between prenatal chlorpyrifos exposure and neurodevelopment in 265 of the CCCEH cohort participants at age 7 years. They described the log of Working Memory Index (WMI) of children as linearly associated with concentration of chlorpyrifos (CPF) in cord blood: Slope = ⁻0.006 (95% CI = ⁻0.01, ⁻0.002). For each standard deviation increase in exposure (4.61 pg/g), they observed a 1.4% reduction in Full-Scale IQ and a 2.8% reduction in Working Memory.

In summary, the EPA's assessment is that the CCCEH study, with supporting results from the other 2 U.S. cohort studies and the seven additional epidemiological studies reviewed in 2015, provides sufficient evidence that there are neurodevelopmental effects occurring at chlorpyrifos exposure levels below that required for AChE inhibition.

5.3 Dose-Response Assessment

5.3.1 Conceptual Approach

As noted above, the agency has historically used 10% inhibition of RBC AChE as the critical effect for deriving PoDs for chlorpyrifos and other OPs. For example, the 2014 HHRA on chlorpyrifos used the PBPK-PD model to derive PoDs that could result in 10% RBC AChE inhibition for multiple exposure scenarios (e.g., worker, dietary, residential). While significant uncertainties remain about the actual exposure levels experienced by mothers and infant participants in the children's health cohorts, it is unlikely that these exposures resulted in RBC AChE inhibition at or above the 10% AChE inhibition response level. For example, as part of the CHAMACOS study, Eskenazi *et al.*, (2004) measured AChE activity and showed that no inhibition in AChE activity were observed. Additionally, following the recommendation of the FIFRA SAP in 2012, the agency conducted a dose reconstruction analysis for pregnant women and young children based on registered residential chlorpyrifos uses available prior to 2000 inside the home (D. Drew *et al.*, D424485, 12/29/2014). The PBPK-PD model using this dose reconstruction analysis indicates that for the highest exposure considered (i.e., indoor broadcast use of a 1% chlorpyrifos formulation), <1% RBC AChE inhibition was produced in pregnant women. While uncertainty exists as to actual chlorpyrifos exposure at (unknown) critical windows of exposure, the agency believes it is unlikely individuals in the epidemiology studies experienced RBC AChE inhibition from their exposure to chlorpyrifos. The 2016 SAP concluded that "epidemiology and toxicology studies suggest there is evidence for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% RBC AChE inhibition (i.e., toxicity at lower doses)." As such, the use of 10% RBC AChE inhibition for deriving PoDs for chlorpyrifos may not provide a sufficiently protective human health risk assessment. Therefore, the agency has endeavored to derive PoDs and uncertainty/safety factors for risk assessment that are protective of both the AChE inhibition and any adverse effects that could occur at lower doses.

As noted, however, the 2016 SAP did not support using the CCCEH cord blood quantitatively in deriving revised PoDs. In their verbal comments, multiple panelists suggested a 'hybrid' approach. In the written report, the SAP did not provide a suggested approach for how the EPA might continue to use the epidemiology data results in a quantitative risk assessment without

attempting to derive the PoD from cord blood data. Specifically, the SAP stated that, given the absence of a particular key window of exposure for the effects shown in the CCCEH study, the EPA should use estimated peak blood concentrations or TWA blood concentrations within the prenatal period as the PoD rather than blood concentrations at delivery. The Panel was also positive and supportive of the agency's use of the PBPK model as a tool for assessing internal dosimetry from the typical OPP exposure scenarios using peer reviewed exposure assessment approaches (e.g., food, water, residential, worker). As such, use of the PBPK model coupled with the typical OPP exposure scenarios to derive PoDs based on TWA blood concentrations, as recommended by the SAP, provide the strongest scientific foundation for moving forward in human health risk assessment for chlorpyrifos. This approach:

- incorporates peer reviewed and accepted inputs for both chlorpyrifos and standard pesticide risk assessment, including: the Residential SOPs[8], the EPA Exposure Factors Handbook 2011 Edition, chlorpyrifos-specific residential exposure modeling inputs and others;
- does not directly rely on quantitative measures of chlorpyrifos in cord blood obtained from the CCCEH, which were the source of uncertainty identified by the 2016 SAP, while still accepting the qualitative findings that chlorpyrifos contributed to the outcomes reported by the CCCEH, which were supported by the 2008 and 2012 SAPs; and
- does not directly rely on quantitative measures of chlorpyrifos in cord blood obtained from the CCCEH, and thus, the lack of access to the raw data from the CCCEH is less of an uncertainty.

The following sections describe the use of the PBPK model to 1) predict TWA of blood concentrations from an exposure scenario likely to be experienced by women in the CCCEH study (indoor use of chlorpyrifos-containing products), and 2) determine the external doses (PoDs for risk assessment) for infants, children, youths, and adults using current exposure assumptions and methodologies (i.e., The 2012 Residential SOPs, and chemical-specific exposure data, etc.) that result in the predicted TWA of blood concentration. The likely indoor use scenario which was experienced by the women in the CCCEH study was derived from the indoor crack and crevice uses of chlorpyrifos; reasoning for selecting this specific scenario is detailed below.

5.3.2 Deriving Internal Concentrations of Chlorpyrifos from Indoor, Crack & Crevice Use

In order to derive a protective PoD for risk assessment from the internal concentrations of chlorpyrifos, the agency reviewed the chlorpyrifos registered uses that would have been available to the CCCEH cohort. The following two risk mitigation actions were the basis for the agency's conclusion that the crack and crevice uses of chlorpyrifos was the most appropriate scenario to assess exposure to the women in the CCCEH cohort in the approximate 1998-2000 timeframe:

- In January 1997, the technical registrants agreed to cancel all broadcast and total release/aerosol foggers containing chlorpyrifos in order to reduce indoor exposures, especially to children and other sensitive groups. The following chlorpyrifos uses were

[8] https://www.epa.gov/sites/production/files/2015-08/documents/usepa-opp-hed_residential_sops_oct2012.pdf

also cancelled: all direct application of pet products including sprays, shampoos, and dips (pet collars not included); and all insecticidal paint additives. Further, all concentrates which required mixing were eliminated, limiting the household consumer's access to only ready-to-use products. Although the above uses were cancelled in 1997, existing stocks could be phased out, or applied until depleted. Indoor crack and crevice (perimeter) and spot treatment as a termiticide uses of chlorpyrifos continued to be registered.

- In June 2000, the technical registrants of chlorpyrifos, agreed to eliminate or phase out nearly all remaining uses that resulted in residential exposure, including: home lawn, crack and crevice, and other indoor uses. Non-residential uses where children could be exposed, such as schools and parks, were also cancelled, with the exception of roach and ant baits in child resistant packaging, and mosquito and fire ant control. For uses that were cancelled, retailers had a stop sale date of December 31, 2001. A phase out of existing stocks was allowed following the 2001 stop sale.

Additionally, in the summer of 2016, OPP contacted several professional pesticide applicators working in New York City apartment buildings around the time of the CCCEH cohort. These professional pesticide applicators recalled that the crack and crevice[9] use was the predominant use around 1998-2000 (D. Friedman, Record of Correspondence, 10/2016). Based on this input, and the mitigation rationale outlined above, the agency has focused on crack and crevice exposures for the 2016 risk assessment.

The 2012 FIFRA SAP (2012) recommended that the EPA conduct a "dose reconstruction" analysis of indoor residential uses to assess potential for RBC AChE inhibition. The dose reconstruction analysis was conducted and presented in the 2014 HHRA[10]. The goal of the dose reconstruction exercise was to estimate upper limit, bounding level exposures, to test the hypothesis of whether RBC AChE at or above the 10% inhibition level used by the agency for typical AChE PoDs may have occurred in the CCCEH cohort. For example, in the dose reconstruction analysis, exposure to the women was assumed to occur 24 hours a day without adjustments for bathing, showering, or leaving the residence for 14 consecutive days. For the 2014 HHRA, residential handler and post-application exposures from indoor broadcast applications resulted in the highest risk estimates and, therefore, were the only exposure estimates presented. The purpose of 2016 analysis for this risk assessment is to predict typical product usage and behaviors thereby deriving more accurate and realistic estimates of exposure compared to the 2014 analysis.

For the 2016 risk assessment, the agency has assessed chlorpyrifos exposures resulting from post-application exposures only. Whyatt *et al.* (2002) reported that many women applied pesticide products themselves, and that majority who reported using pesticide products used them at least once per month. However, as the agency has shown in the 2014 dose reconstruction analysis, post-application exposures are greater in magnitude than exposures which occur during an application. Therefore, the assessment of post-application exposure ensures that the highest potential exposures are evaluated. Specifically, the 2016 risk assessment

[9]Per the 2012 Residential SOPs, a crack and crevice application is defined as application of pesticides with the use of a pin stream nozzle, into cracks and crevices in which pests hide or through which they may enter a building. Such openings commonly occur at expansion joints, between different elements of construction, and between equipment and floors.

[10] The methods, algorithms, and exposure data used to conduct the dose reconstruction analysis can be referenced in Appendix 10 of the 2014 HHRA.

focuses on the post-application exposures from the chlorpyrifos in crack and crevice use since this was the predominant application type during the time of the CCCEH cohort.

The dose reconstruction in the 2016 risk assessment is based on the methods outlined in the 2012 Residential SOPs[11] which describe specific algorithms and inputs, on a scenario-specific basis.[12] Appendix 10 of the 2014 HHRA (D. Drew *et al.*, D424485, 12/29/2014) can be referenced for a description of the methods, algorithms, and inputs used. Specifically, the 2012 Residential SOPs[13] have been used to predict the range of potential exposures which could have occurred to individuals in the cohort for crack and crevice hard surface and carpet treatments. The present analysis uses the same chemical-specific exposure data inputs recommended in the 2012 Residential SOPS (*i.e.*, the fraction of chlorpyrifos residues transferred from treated carpet and hard surfaces to the exposed individual; and exposure data used to derive the liquid formulation transfer coefficient (TC)). Additionally, chemical-specific exposure data were used to define the concentrations of chlorpyrifos present in air following indoor applications. The differences between the previous dose reconstruction and the present analysis are: (1) the exposure duration was 24 h/day for the 2014 dose reconstruction analysis, and 2 h/day for the present analysis; (2) predicted endpoint for the dose reconstruction analysis was the peak RBC AChE inhibition level during the 14 days post-application, and the predicted endpoint for the present analysis was time-weighted average of chlorpyrifos concentrations in blood; (3) no shower was assumed to occur over the 14-day exposure period for the dose reconstruction analysis, whereas a daily shower is assumed to occur for the present analysis; (4) the total exposure duration was 14 days in the dose reconstruction analysis, and 30 days in the present analysis. The assumption that women followed in the CCCEH cohort showered immediately after exposure leads to significantly more conservative estimates of risk assessment PoDs (i.e., neurodevelopmental effects may have occurred at lower exposure levels when assuming that the women showered after daily exposure vs. when it is assumed that the women did not shower after daily exposure); however, since other inputs (e.g., 50% of the body exposed) lead to less conservative PoD estimates, the combination of inputs used to estimate exposures is expected to reasonably approximate exposures to these women resulting in reasonable risk assessment PODs.

For the 2016 risk assessment, the agency assumed a once daily shower occurred immediately following exposure activities. The PBPK model simulation were conducted for a 30-day post-application in the crack & crevice scenario. Daily exposure durations for post-application dermal contact with carpets and hard surfaces were selected based on the recommendation in the 2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment[14] (herein referred to as the 2012 Residential SOPs). Specifically, for adults, the recommended exposure durations for post-application dermal contact are 8 and 2 hours daily for carpets and hard surfaces, respectively. These values are based on the EPA Exposure Factors Handbook 2011[15] Edition that provides information on the total time spent in a residence and time spent in various rooms within a residence. The hard surface exposure scenario resulted the highest estimated exposures and, therefore, was selected for PBPK model PoD derivation. Additionally, chlorpyrifos residues were assumed to dissipate 10% daily; that is, the total amount of residue

[11] https://www.epa.gov/sites/production/files/2015-08/documents/usepa-opp-hed_residential_sops_oct2012.pdf
[12] The 2012 Residential SOPs were subjected to peer review by FIFRA SAP in October 2009. http://www.regulations.gov/#!docketBrowser;rpp=50;po=0;D=EPA-HQ-OPP-2009-0516
[13] https://www.epa.gov/sites/production/files/2015-08/documents/usepa-opp-hed_residential_sops_oct2012.pdf
[14] http://www.epa.gov/pesticides/science/residential-exposure-sop.html
[15] http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252

available for transfer from the treated floor is assumed to reduce by 10% for each subsequent day of exposure until the end of the 30th day prior to the next application. The 10% value was based on an evaluation of all available chlorpyrifos-specific floor residue data. For all post-application exposure scenarios a female bodyweight reflective of all trimesters of pregnancy, 75 kg, was assumed to reflect the population of interest from the CCCEH cohort. This value was derived from the EPA Exposure Factors Handbook 2011 Edition (adult female: Tables 8-3 through 8-5; body weight of pregnant women: Table 8-29).

The results of the 2016 dose reconstruction assessment of the post-application exposures following contact with hard surfaces following indoor chlorpyrifos crack and crevice treatment is presented in Table 5.3.2.

Table 5.3.2. Residential Post-application Exposures to Women in the CCCEH Cohort Following Indoor Chlorpyrifos Crack and Crevice Treatment.

Exposure Scenario	Formulation	Deposited Residue[1] (µg/cm^2)	Fraction Transferred[2]	Transferable Residue[3] (µg/cm^2)	Transfer Coefficient (cm^2/hr)	Exposure Time (hr/day)	Dermal Dose[4] (mg/kg/day)	Airborne Concentration of Chlorpyrifos[5] (mg/m^3) - Day of Application
Crack and Crevice (Hard Surfaces)	1% PCO Crack and Crevice Application	0.30	0.13	0.039	6,800	2	0.00707	0.00089

1 Estimated based on the recommendations of the 2012 Residential SOPs: Indoor Environments SOP.
2 Chlorpyrifos-specific fraction transfer as recommended in the 2012 Residential SOPs: Indoor Environments SOP (Table 7-9; Arithmetic Mean).
3 Transferable Residue (µg/cm^2) = Deposited Residue (µg/cm^2) * Fraction Transferred (unitless)
4 Dermal Dose (mg/kg/day) = Transferable Residue (µg/cm^2) * Transfer Coefficient (cm^2/hr) * Exposure Time (hr/day) * Conversion Factor (0.001 mg/µg)
5 Average airborne concentration of chlorpyrifos from crack and crevice on the day of product application as determined from 3 literature studies and 1 registrant submitted study.

The PBPK model-predicted time course of chlorpyrifos concentrations in blood based on the crack and crevice scenario is provided in Figure 1. The predicted TWA of chlorpyrifos concentration in blood from this scenario was 0.004 µg/L, shown as the solid horizontal line in Figure 1.

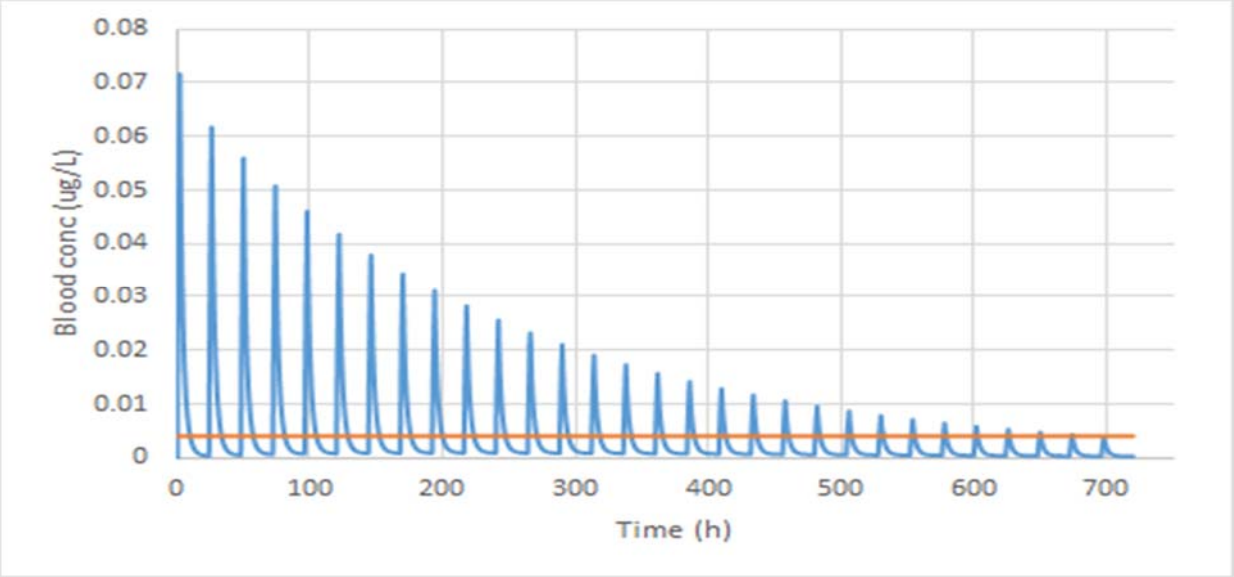

Figure 1: The PBPK model-predicted time course of chlorpyrifos concentrations in blood based on the crack and crevice scenario. The predicted TWA of chlorpyrifos concentration in blood (0.004 µg/L) is shown by the solid line.

5.3.3 Determining PoDs

In typical risk assessments, PoDs are derived directly from laboratory animal studies and inter- and intra-species extrapolation is accomplished by use of 10X factors. In the case of chlorpyrifos, the PBPK model for chlorpyrifos was used as a data-derived extrapolation approach to estimate individual PoDs for pregnant women and children. As noted above, the PBPK model was first used to predict, from the crack and crevice post-application scenario, the TWA of chlorpyrifos concentration in blood as the internal dose metric for deriving PoDs in the subsequent analyses.

For the 2014 HHRA (D. Drew *et. al*, D424485, 12/29/2014), the EPA developed PoDs based on AChE inhibition to protect against cholinergic toxicity; such cholinergic toxicity could occur to any lifestage if exposure is sufficiently high. As such, in 2014, the EPA evaluated the spectrum of lifestages from the fetus through adulthood. Fetuses may be exposed to chlorpyrifos through the mother while infants and children may be exposed directly. Studies in laboratory animals do not suggest any specific critical period or lifestage, but instead suggest pre- and post-natal periods of susceptibility. The EPA acknowledges that the epidemiology literature regarding associations between post-natal (infancy, childhood) biomarker metrics and neurodevelopmental outcomes is limited to the Bouchard *et al.*, (2010) study, a cross-sectional study that observed positive association between attention and behavior problems and total dialkyl phosphate metabolites (DAPs) and dimethyl alkylphosphate metabolites (DMAPs), using urinary National Health and Nutrition Examination Survey (NHANES) data in children 8–15 years old. The other studies which evaluated postnatal biomarker metrics and neurodevelopment outcomes have found no statistically significant associations. Specifically, postnatal exposure to OPs (measured as DAPs) has been assessed in the CHAMACOS cohort (Eskenazi *et al.*, 2007; Young *et al.*,

2005; Bouchard *et al.*, 2011), two other cross-sectional studies (Guodong *et al.*, 2012; Oulhote and Bouchard, 2013) and Engel *et al.*, (2016). Despite the limited epidemiological evidence from postnatal exposure, the EPA is proposing to use the TWA as the most relevant source of information for deriving a PoD specific for chlorpyrifos for fetuses, infants, and children. Consistent with the advice from the 2016 SAP, the EPA believes that the CCCEH results are directly relevant to fetal exposure and newborns; however, the EPA acknowledges they may be less relevant to older infants, toddlers, and children. The EPA has conducted exposure assessments for all typical age groups for completeness and acknowledges that the exposure and risk assessment results for females 13-49 years old are the most relevant to the CCCEH data.

The PBPK model accounts for pharmacokinetic characteristics to derive age, duration, and route specific PoDs (Table 5.3.3.3). Separate PoDs have been calculated for dietary (food, drinking water), residential, and occupational exposures by varying inputs on types of exposures and populations exposed to obtain a predicted time-weighted average of 0.004 µg/L chlorpyrifos in blood using inputs specific to each scenario (i.e., duration exposed, amount consumed, etc). Specifically, the following characteristics have been evaluated: route (dermal, oral, inhalation); body weights which vary by life-stage; exposure duration (hours per day, days per week); and exposure frequency [events per day (eating, drinking)].

To derive a PoD for each non-dietary and dietary exposure scenario and subpopulation, the appropriate body weight for each age group or sex was taken from the Exposure Factors Handbook (USEPA, 2011) (for occupational exposures) or from the NHANES/What We Eat in America (WWEIA) Survey[16] (for dietary exposures). All body weights used are consistent with those assumed for typical pesticide dietary, occupational, and residential exposure assessments and shown in Table 5.3.3.1.

Table 5.3.3.1. Body Weight Assumptions Incorporated into PBPK Model for Chlorpyrifos.

Exposure Scenario	Exposure Pathway	Population & Body Weight (kg)				
		Infants (< 1 yr old)	Young Children (1 - 2 years old)	Children (Residential:6-11 years old; Dietary:6-12 years old)	Youths (Residential:11-16 years old; Dietary:13-19 years old)	Females (13 – 49 years old)
Dietary	Food and Drinking Water	4.8[1]	12.6[2]	37.1[2]	67.3[2]	72.9[2]
Residential (Golfers)	Dermal			32[5]	57[6]	69[4]
Residential (Mosquitocide Application)	Dermal, Oral, Inhalation		11[3]			
Residential (Bystander/ Volatilization Assessment)	Inhalation		11[3]			
Occupational	Dermal, Inhalation					

1 For infants from birth to < 1 year old, the agency has selected the body weight for the youngest age group, birth to < 1 month old, 4.8 kg (Exposure Factors Handbook, Table 8-3, mean body weight for the birth to < 1 month age group).
2 NHANES/WWEIA
3 Exposure Factors Handbook, Table 8-3, mean body weight for the 1 to < 2 year old age group.

[16] http://www.ars.usda.gov/Services/docs.htm?docid=13793

4 Exposure Factors Handbook, Table 8-5, mean body weight for females 13 to < 49 years old.
5 Exposure Factors Handbook, Table 8-3, mean body weight for the 6 to < 11 year old age group.
6 (Exposure Factors Handbook, Table 8-3, mean body weight for the 11 to < 16 year old age group).

Table 5.3.3.2 shows the durations (days) of exposure included in the PBPK model to derive PoDs.

Table 5.3.3.2. Days of Exposure Assumptions Incorporated into PBPK Model for Chlorpyrifos.

Exposure Scenario	Exposure Pathway	Population & Days of Exposure				
		Infants (< 1 yr old)	Young Children (1 - 2 years old)	Children (Residential:6-11 years old; Dietary:6-12 years old)	Youths (Residential:11-16 years old; Dietary:13-19 years old)	Females (13 – 49 years old)
Dietary	Food and Drinking Water	21	21	21	21	21
Residential (Golfers)	Dermal			21	21	21
Residential (Mosquitocide Application)	Dermal, Oral, Inhalation		21			
Residential (Bystander/ Volatilization Assessment)	Inhalation		1 & 21			
Occupational	Dermal, Inhalation					

To derive the dietary exposure PoDs, dietary exposure was estimated daily for 21 days. For drinking water exposures, the daily water consumption volume was set to 0.688557 L for infants, children between 1-2 year old, and children 6-12 years old; 1.71062 L for youths 13-19 years old and female adults. Infants and children were assumed to consume water six times a day; youths and female adults were assumed to consume water four times a day. For food exposures, the eating event was set to one meal per day. The daily volumes consumed and number of daily consumption events for all populations are mean values by age group based on USDA's WWEIA. The mean daily water consumption amounts for children 1- 2 years old (0.35 L) and children 6-12 years old (0.58 L), were less than that for infants (0.688557 L); the infant daily water consumption volume was selected for all child sub-populations to be protective. For youths 13-19 years old, the mean daily water consumption amount (0.93 L) was less than that for the female adults (1.71062 L); therefore, the adult daily water consumption was selected for both subpopulations to be protective.

For all residential dermal exposures to chlorpyrifos, the fraction of skin in contact with chlorpyrifos was set to 50% to reflect uncovered skin areas for adults and children wearing shorts and a tee shirt. A daily shower (i.e., washing off the chlorpyrifos) was assumed immediately following chlorpyrifos exposure. All residential exposures were set to be continuous for 21 days. For residential exposures via golfing on treated turf, the daily exposure time is assumed to be 4 hours/day; for residential exposures via contact with turf following public health mosquitocide application, the daily exposure duration is assumed to be 1.5 hours for ground applications and 1 hour for aerial applications. For residential inhalation exposures following public health mosquitocide application, the exposure duration was set to 1 hour per

day. These exposure times selected were based on those recommended in the 2012 Residential SOPs. For residential bystander exposures from volatilization following treatment of nearby fields, the inhalation exposure time was set to 24 hours per day. For inhalation exposures following mosquitocide application and from volatilization, the inhalation rates were set to 0.33 m^3/hour for children 1 to < 2 years old and 0.64 m^3/hour for adults.

In addition to dietary and residential exposures, the PBPK model was also used to estimate PoDs resulting in a time-weighted average of 0.004 µg/L chlorpyrifos in blood following occupational exposures (Table 5.3.3.3). Dermal exposures for workers assumed even distribution across the entire body surface area. A daily shower (i.e., washing off the chlorpyrifos) was assumed following chlorpyrifos exposure. The worker was assumed to be a female adult between the ages of 13 to 49, and had a body weight of 69 kg. This worker is exposed to chlorpyrifos either via inhalation or skin for 8 hours/day, 5 days/week, for a total of 21 days.

Table 5.3.3.3. PBPK Model-Predicted Chlorpyrifos Point of Departures (PoDs) Corresponding to a Time-Weighted Average of 0.004 µg/L Chlorpyrifos in Plasma*.

Exposure Scenario	Exposure Pathway	Infants (< 1 year old)	Young Children (1 - 2 years old)	Children (Residential:6-11 years old; Dietary:6-12 years old)	Youths (Residential:11-16 years old; Dietary:13-19 years old)	Females (13 – 49 years old)
Dietary	Drinking Water (µg/kg/day)	1.4	3.2	7.1	4.8	5.1
	Food (µg/kg/day)	0.2	0.17	0.13	0.12	0.12
Residential (Golfers)	Dermal (µg/kg/day)			2.2	1.4	1.3
Residential (Mosquitocide Application)	Dermal (µg/kg/day)		14.9			3.4
	Oral (µg/kg/day)		0.17			
	Inhalation (concn. in air mg/m^3)[1]		*Aerial:* 0.00165 *Ground:* 0.0011			*Aerial:* 0.0051 *Ground:* 0.0034
Residential (Bystander/ Volatilization Assessment)	Inhalation (concn. in air mg/m^3)		*Steady State:* 0.00068 *Acute:* 0.0013			*Steady State:* 0.00021 *Acute:* 0.004
Occupational	Dermal (µg/kg/day)					0.47
	Inhalation (concn. in air mg/m^3)					0.0011

*PoDs and exposure and risk estimates for females 13-49 yrs covers all youths >13 yrs.

1. PBPK model inputs for inhalation mosquitocide scenarios differ based on the exposure scenario being assessed. Since the AgDISP (v8.26) model predicts the 1 hour average air concentration following aerial applications, the PBPK-PD was model was run assuming 1 hr of inhalation exposure/day, 7 days/week, and 21 days of exposure. For ground based ULV applications, risks are estimated based on the inhalation exposure duration for time spent outdoors (1.5 hours/day) and, therefore, the PBPK-PD model was run assuming 1.5 hours of inhalation exposure/day, 7 days/week, 21 days of exposure.

5.3.4 Uncertainty, Extrapolation, & FQPA Safety Factors

The TWA blood level resulting from chlorpyrifos exposure from the crack and crevice scenario

is considered a LOAEL rather than a NOAEL, since this is the exposure level likely to be associated with neurodevelopmental effects reported in the CCCEH study. In situations where the agency selects a PoD from a study where a NOAEL has not been identified, the EPA generally will retain the FQPA SF of 10X to account for the uncertainty in using a LOAEL. In the 2016 revised risk assessment this is being done for chlorpyrifos. The 2016 revised risk assessment also applies a 10X uncertainty factor for intraspecies variability because of the lack of sufficient information to reduce or remove this factor. Typically, the agency uses animal studies for selection of PoDs and, as such, retains a 10X interspecies factor for extrapolation of the animal data to assess human health. However, with use of the PBPK-PD model which accounts for the pharmacokinetic and pharmacodynamic differences between animals and humans to derive PoDs, it is appropriate to reduce the interspecies factor to 1X. Therefore, the total uncertainty factors for chlorpyrifos in this 2016 risk assessment are 100X (10x for intra-species extrapolation and 10x for the FQPA 10 safety factor).

6.0 Dietary Exposure and Risk Assessment

HED had previously conducted both acute and steady state dietary (food only) exposure analyses for chlorpyrifos using DEEM and Calendex software with the Food Commodity Intake Database (FCID) (D. Drew *et al.*, D424486, 11/18/2014), respectively.

For the current assessment, the steady state exposure values resulting from the 2014 dietary assessment are compared to the updated PBPK-derived steady state Population Adjusted Dose (ssPAD). When the dietary exposure exceeds 100% of the ssPAD there is a potential risk concern.

Since the steady state dietary assessment is protective of any acute food exposures, only the results of the steady state assessment are discussed herein. The steady state analysis calculated exposures for the sentinel populations of infants <1 year old, children 1-2 years old, youth 6-12 years old, and females 13-49 years old.

All details pertaining to the assumptions, data inputs, and exposure outputs for the dietary analysis may be found in the 2014 dietary assessment memorandum (D. Drew *et al.*,D425586, 11/18/2014).

6.1 Food Residue Profile

The residue of concern for tolerance expression and risk assessment in plants (food and feed) and livestock commodities is the parent compound chlorpyrifos. Based on the available crop field trials, metabolism studies, and PDP monitoring, the cholinesterase inhibiting metabolite, chlorpyrifos oxon, would be not be present in edible portions of the crops, or in livestock tissue or milk and, therefore, is not included in the food assessment.

The steady state dietary exposure analysis is highly refined. The large majority of food residues used were based upon USDA's PDP monitoring data except in a few instances where no appropriate PDP data were available. In those cases, field trial residues or tolerance level residues were assumed. The Biological & Economic Analysis Division (BEAD) provided

percent crop treated information in the Screening Level Usage Analysis **(**SLUA; May 1, 2014). Food processing factors from submitted studies were used as appropriate. All commodities with current U.S. tolerances for residues of chlorpyrifos are included in this assessment (40 CFR§180.342).

6.2 Steady State Dietary (Food Only) Exposure and Risk Estimates

The steady state dietary (food only) exposures for chlorpyrifos are of concern at the 99.9th percentile of exposure for all population subgroups analyzed. Children (1-2 years old) is the population subgroup with the highest risk estimate at 14,000% of the ssPAD$_{food}$.

Table 6.2. Steady State Dietary (Food Only) Exposure and Risk Estimates for Chlorpyrifos.

Population Subgroup	$_{SS}$PoD$_{food}$[1] (µg/kg/day)	ssPAD$_{food}$[2] (µg/kg/day)	Food Exposure[3] (µg/kg/day)	% of ssPAD$_{food}$
Infants (< 1 yr)	0.20	0.002	0.186	9,300
Children (1-2 yrs)	0.17	0.0017	0.242	14,000
Youths (6-12 yrs)	0.12	0.0012	0.128	11,000
Adults (Females 13-49 yrs)	0.12	0.0012	0.075	6,200

1 Steady state point of departure; daily dose predicted by PBPK-PD for steady state (21 day) dietary (food) exposures (see Table 5.3.3.3 for PoDs).
2 ssPAD= Steady state population adjusted dose = PoD (Dose predicted by PBPK model ÷ total UF; Total uncertainty factor =100X (10X intraspecies factor and 10X LOAEL to NOAEL extrapolation factor).
3 Steady state (21 day) food-only exposure estimates from Calendex (at 99.9th percentile).

6.3 Steady State Dietary (Food Service/Food Handling Establishments) Exposure and Risk Estimate

There are chlorpyrifos uses in food handling establishments (FHE) where food and food products are held, processed, prepared or served. These may include areas such as boxcars, shipping containers, and warehouses. FHE uses in restaurants, or similar service areas where food is prepared and served, may also be referred to as *food service establishment* (FSE) uses. There are no tolerances for the chlorpyrifos uses in FHEs except for the specific use of chlorpyrifos in FSEs as stated in the 40 CFR§180.342 (a) (3):

A tolerance of 0.1 part per million is established for residues of chlorpyrifos, per se, in or on food commodities (other than those already covered by a higher tolerance as a result of use on growing crops) in food service establishments where food and food products are prepared and served, as a result of the application of chlorpyrifos in microencapsulated form.

Typically, where there are established tolerances for FSE (or FHE) uses, anticipated residues for *all* foods would be included in the dietary assessment along with the residues on the foods with crop tolerances. The food only exposures in Section 6.2do not incorporate potential exposure from residues that may result on foods from FSE uses and, therefore, may underestimate actual exposures. A previous dietary risk assessment included a chronic analysis for FSE uses (D. Soderberg, D388166, 6/11/2011). This analysis was based on a BEAD estimate of < 2% of

establishments treated with chlorpyrifos and half the analytical limit of detection (½ LOD; 0.01 ppm) based on all nondetectable residues in a chlorpyrifos FHE study. That analysis resulted in a chronic dietary exposure of 0.009 µg/kg for children ages 1-2 years old (highest exposed population subgroup). HED has used this exposure value to compare to the ssPAD for children ages 1-2 years old. For the FSE uses alone, the children ages 1-2 years old steady state dietary (food only) exposures for chlorpyrifos are of concern, with an estimated risk of 530% of the ssPAD.

6.4 Dietary Drinking Water Risk Assessment

The total dietary exposure to chlorpyrifos is through both food and drinking water. EFED has provided a revised drinking water assessment (DWA) for chlorpyrifos (R. Bohaty, D432921, 04/14/2016) which includes the updated EDWCs for dietary risk assessment. A DWLOC approach is used to calculate the amount of exposure available in the total dietary 'risk cup' for chlorpyrifos in drinking water after accounting for chloropyrifos exposure from food. This DWLOC is then compared to the EDWC to determine if there is a risk of concern for drinking water exposures (See D. Drew, D424485, 12/29/2014 for details on the DWLOC approach and calculations). However, because the dietary risks from food alone are of concern (exceed the ssPAD), it is not possible to calculate a DWLOC; essentially the steady state DWLOC is '0' after accounting for food exposures.

Hypothetically, if there were no exposure to chlorpyrifos from food, and the entire dietary 'risk cup' was available for drinking water, the resulting steady state DWLOC for infants (the most highly exposed population subgroup for water) would be 0.014 ppb. An EDWC at or exceeding this concentration would be considered a risk of concern for exposures to chlorpyrifos in drinking water.

7.0 Residential (Non-Occupational) Exposure/Risk Characterization

Residential exposures to chlorpyrifos are currently expected from homeowner use. Formulations/use sites registered for homeowner use include a granular ant mound use and roach bait in child-resistant packaging. Additionally, chlorpyrifos is labeled for public health aerial and ground-based fogger ULV mosquito adulticide applications and for golf course turf applications. All residential exposures and risks were previously assessed in support of the 2014 HHRA (W. Britton, D424484, 12/29/2014). The previous assessment included evaluation of residential post-application risks from playing golf on chlorpyrifos-treated courses and from exposures which can occur following aerial and ground-based ULV mosquito adulticide usage. The potential for residential exposures from the roach bait product was determined to be negligible. Further, residential exposures from the ant mound use were also determined to be negligible since these products can only be applied professionally and direct exposure with treated ant mounds is not anticipated.

In addition to the assessment of residential exposure, the potential for post-application exposures to residential bystanders who live on, work in, or frequent areas adjacent to treated fields from spray drift and volatilization were also evaluated and presented in the 2014 HHRA.

The previously assessed residential post-application, residential bystander/volatilization, and non-occupational spray drift risk estimates have been updated to incorporate the approach applied for PBPK-derivation of PoDs for infants, children, and adults based on the exposures estimated from the indoor crack and crevice uses of chlorpyrifos during the time of the CCCEH cohort.

7.1 Residential Handler Exposure/Risk Estimates

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are addressed somewhat differently by HED as homeowners are assumed to complete all elements of an application without use of any protective equipment.

Based upon review of all chlorpyrifos registered uses, only the roach bait products can be applied by a homeowner in a residential setting but the application of roach bait products has not quantitatively assessed because these exposures are negligible. The roach bait product is designed such that the active ingredient is contained within a bait station which eliminates the potential for contact with the chlorpyrifos containing bait material. Therefore, updated residential handler risks are not required for these uses.

7.2 Residential Post-application Exposure/Risk Estimates

Residential post-application exposures are likely from being in an environment that has been previously treated with chlorpyrifos. Chlorpyrifos can be used in areas frequented by the general population including golf courses and as an aerial and ground-based ULV mosquito adulticide applications made directly in residential areas. Post-application exposure from residential ant mound treatment was assessed qualitatively as addressed above because negligible exposures are anticipated.

All of the residential post-application exposure scenarios, data and assumptions, and algorithms used to assess exposures and risks from activities on golf course turf following chlorpyrifos application are the same as those used in the 2014 HHRA and ORE assessment. Additionally, this updated assessment makes use of the same chemical-specific turf transferable residue (TTR) data used previously to assess exposures and risks from golfing. Only the PoDs and LOCs have changed.

The residential post-application exposures and risks resulting from aerial and ground-based ULV mosquito adulticide applications have also been updated to reflect the updated PoDs and LOCs. However, the risks from the exposure scenarios have also been updated to reflect 1) the current default deposition fraction recommended for ground applied ULV mosquitocides (i.e., 8.7 percent of the application rate vs the previous 5 percent) and 2) several iterations of aerial applications modeled assuming differing winds speeds and release heights allowed by chlorpyrifos mosquitocide ULV labels. All other inputs and algorithms used for assessment of these exposure scenarios in 2014 remain the same, including the use of the chemical-specific TTR data. The AgDISP (v8.2.6) model input parameters, outputs, and the algorithms used to estimate residential post-application exposures following aerial and ground-based ULV

mosquitocide application can be found in Appendix A.

Default deposition fraction for ground applied ULV mosquitocides: Previously, an off-target deposition rate of 5 percent of the application rate was used by HED to evaluate ground-based ULV applications (i.e., 5 percent of the target application rate deposits on turf). This recommendation was based on data from Tietze *et al.,* and Moore *et al.* In a 2013 analysis (C. Peck, D407817, 3/28/2013), the Environmental Fate and Effects Division (EFED) reviewed eight published studies on ground ULV application in which deposition was measured. The studies varied in collection media (i.e., grass clippings and coupons), distance from application or spray head (ranging from 8 meters to 500 meters), and chemical measured (i.e., fenthion, malathion, naled, and permethrin). The analysis included the Moore *et al.,* and Tietze *et al*., studies cited above. After considering the available data, HED has determined that an off-target deposition rate of 8.7 percent of the application rate may be used by HED to evaluate ground-based ULV applications (i.e., 8.7 percent of the target application rate deposits on turf). This value is the 90 percent upper confidence limit on the mean and is slightly higher than the mean values from all the data points observed in the studies (7.1%, n= 94). The adjusted application rate was then used to define TTR levels by scaling the available TTR data as appropriate.

Aerial application wind speed, volume median diameter, and release height: Previously, HED used the AgDISP (v8.2.6) model to assess deposition and air concentrations from aerial ULV applications assuming a 1 mph wind speed, volume median diameter is less than 60 µm (Dv 0.5 < 60 µm), and 300 foot release height. For this updated assessment, bounding risks have been estimated using the model based on a range of labeled application parameters. Lower spray height and lower wind speeds, and a greater Dv 0.5, results in the worst case potential exposures, or reduced potential for spray drift and, as a result, a greater deposition fraction and 1 hour average concentration. Therefore, estimated dermal and inhalation risks would be greater under these application conditions. The reverse is true for the best-case modeling scenario.

- Worst-case - 1 mph wind speed, Dv 0.5 = 60 µm, and 75 foot release height; and
- Best-case - 10 mph wind speed, Dv 0.5 = 40 µm, and 300 foot release height.

The following inputs were used for AgDISP (v8.26) modeling of chlorpyrifos ULV aerial applications.

Table 7.2.1. AGDISP Inputs (v8.26): Chlorpyrifos Mosquitocide ULV Aerial Application.

Input Parameters	Inputs to include in the AgDISP model	Notes/Comments
Application Method	Aerial	Default
Aircraft	Air Tractor AT-401	Default
Release Height	75, 300 Feet minimum release	Label allows a release height ranging from 75 to 300 feet.
Spray Lines	20 Reps	Default
Application Technique	Liquid	Default
Application Technique *Nozzles*	3; Extent 76.3%; Spacing 18.7 ft	Default
Application Technique *Drop Size Distribution*	User defined Parametric; $D_{V0.5}$: 40, 60 µm; and relative span: 1.4.	A $D_{v0.5}$ value of < 60 µm is allowable on the label. A $D_{v0.5}$ value of < 40 µm was modeled to estimate a lower droplet size

Table 7.2.1. AGDISP Inputs (v8.26): Chlorpyrifos Mosquitocide ULV Aerial Application.		
Input Parameters	**Inputs to include in the AgDISP model**	**Notes/Comments**
	no conversion to Malvern Drop Size Distribution	as is typically used for ULV aerial application.
Swath Width	500 feet	Default
Swath Displacement	Worst case application parameters: -130 feet Best case application parameters: 3,729 feet	The modeled spray deposition shows the peak deposition to be at a distance other than 0 feet. Therefore, the swath displacement w changed to the horizontal distance from the y axis where the peak deposition occurred and then the air concentration value was selected at this distance.
Meteorology	Wind type: single height Wind speed: 1, 10 mph Wind direction: -90 deg Temperature: 85 F° Relative humidity: 50%	No wind speed was identified on the label. The wind speeds of 1 and 10 mph were modeled to represent a reasonable range of wind speeds typical of ULV aerial applications.
Spray Material	Name: Oil Spray Material Evaporates: Yes Spray volume rate: 1.5 (gal/A) Active Fraction: 0.1936 Nonvol Fraction: 1	Spray material criteria as defined by the product label.
Atmospheric Stability	Overcast	Default
Surface	Upslope angle: 0 deg Sideslope angle: 0 deg Canopy: None	Default
Transport	Distance: 0 feet	Default
Advanced	Default Swatch offset: 0 Swath Specific Gravity carrier: Oil Specific Gravity active and additive= 0.929 Evaporation Rate: 84.76	Inputs based on criteria as defined by the product label.

Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates

A summary of risk estimates is presented in Tables 7.2.2 through 7.2.8 below.

All residential post-application exposure scenarios assessed for playing golf on chlorpyrifos-treated courses, including all relevant populations and in consideration of all TTR data state sites, result in risks of concern (i.e., MOEs are < 100). Further, all residential post-application exposure scenarios assessed following aerial and ground ULV mosquitocide application result in risks of concern. All risk estimates are provided in Appendix B.

Table 7.2.2. Residential Post-application Non-cancer Exposure and Risk Estimates from Playing Golf on Chlorpyrifos-Treated Courses.						
Lifestage	**Post-application Exposure Scenario**		**Application Rate[1]**	**State (TTR Data)**	**Dose (mg/kg/day)[2]**	**MOEs[3]**
	Use Site	**Route of Exposure**				
Adult	Golf Course	Dermal	1.0	CA	0.010	0.13

Table 7.2.2. Residential Post-application Non-cancer Exposure and Risk Estimates from Playing Golf on Chlorpyrifos-Treated Courses.						
Lifestage	**Post-application Exposure Scenario**		**Application Rate[1]**	**State (TTR Data)**	**Dose (mg/kg/day)[2]**	**MOEs[3]**
	Use Site	**Route of Exposure**				
(Females)	Turf		(Emulsifiable Concentrate)	IN	0.0069	0.19
				MS	0.012	0.11
				Mean	0.0095	0.14
Youths 11 to < 16 years old				CA	0.010	0.14
				IN	0.0070	0.20
				MS	0.012	0.12
				Mean	0.0096	0.15
Children 6 to < 11 years old				CA	0.012	0.19
				IN	0.0082	0.27
				MS	0.014	0.16
				Mean	0.011	0.20
Adult (Females)			1.0 (Granular)	CA	0.0088	0.15
Youths 11 to < 16 years old					0.0088	0.16
Children 6 to < 11 years old					0.010	0.21

1 Based on the maximum application rates registered for golf course turf use.
2 Dose (mg/kg/day) equations for golfing are provided in Appendix B of the 2014 HHRA. For dose estimation from exposures to golfing on treated turf TTR data was used. Doses have been presented for all State sites, including the mean of all State sites.
3 MOE = PoD (mg/kg/day) ÷ Dose (mg/kg/day). See Table 5.3.3.3 for PODs.

Table 7.2.3. Residential Post-application Inhalation Steady State Exposure Estimates from Chlorpyrifos ULV Aerial Mosquitocide Application - AgDISP Model.			
Application Parameters	**Population**	**Air Concentration Estimate (mg/m^3)[1]**	**MOE[2]**
1 mph Wind Speed Dv 0.5 = 60 µm 75 Foot Release Height	Adults	0.0047	**1.1**
	Children 1 to <2 years old		**0.35**
10 mph Wind Speed Dv 0.5 = 40 µm 300 Foot Release Height	Adults	0.00070	**7.3**
	Children 1 to <2 years old		**2.4**

1 Air concentration estimate modeled using AGDISP v8.2.6 at breathing height of adults and children.
2 MOE = PoD (mg/m^3) ÷ Dose (mg/m^3). See Table 5.3.3.3 for PODs.

Table 7.2.4. Residential Post-application Inhalation Steady State Exposure Estimates from Chlorpyrifos ULV Ground Mosquitocide Application - WMB Model.		
Population	**Air Concentration Estimate (mg/m^3)[1]**	**MOE[2]**
Adults	0.0013	**0.66**
Children 1 to <2 years old		**0.21**

1 Air concentration estimate modeled using the well mixed box model. The inputs and algorithms used are presented in Appendix C of the 2014 HHRA.
2 MOE = PoD (mg/m^3) ÷ Dose (mg/m^3). See Table 5.3.3.3 for PODs.

Table 7.2.5. Residential Post-application Dermal Steady State Exposure Estimates Resulting from Chlorpyrifos Aerial ULV Mosquitocide Application.

Application Parameters	Lifestage	Application Rate (lb ai/A)	AgDISP Deposition Fraction[1]	Adjusted TTR[2] (µg/cm^2)	Dermal Dose[3] (mg/kg/day)	MOE[4]
1 mph Wind Speed Dv 0.5 = 60 µm 75 Foot Release Height	Adults	0.010	1.0	0.00038	0.0015	**2**
	Children 1 to < 2 Years Old				0.0026	**6**
10 mph Wind Speed Dv 0.5 = 40 µm 300 Foot Release Height	Adults	0.010	0.086	0.000033	0.00013	**27**
	Children 1 to < 2 Years Old				0.00022	**68**

1 Aerial fraction of mosquitocide application rate deposited on turf as determined using AgDISP model v8.2.6.
2 TTR_t (µg/cm^2) = [(Day 0 Residue from MS TTR study (µg/cm^2) x Application Rate (0.010 lb ai/A)) / Application Rate of MS TTR Study (3.83 lb ai/A))] * AgDISP Deposition Fraction
3 Dermal Dose (mg/kg/day) = [(TTR_t (µg/cm^2) * CF1 (0.001 mg/µg) * Transfer Coefficient (180,000 cm^2/hr, adults; 49,000 cm^2/hr, children) * ET (1.5 hrs))] ÷ BW (kg)
4 MOE = PoD (mg/kg/day) ÷ Dose (mg/kg/day). See Table 5.3.3.3 for PODs.

Table 7.2.6. Residential Post-application Dermal Steady State Exposure Estimates Resulting from Chlorpyrifos ULV Ground Mosquitocide Application.

Lifestage	Application Rate (lb ai/A)	Deposition Fraction[1]	Adjusted TTR[2] (µg/cm^2)	Dermal Dose[3] (mg/kg/day)	MOE[4]
Adults	0.010	1.0	0.00038	0.0015	**26**
Children 1 to < 2 Years Old				0.0026	**67**

1. Ground fraction of mosquitocide application rate deposited on turf as determined using eight published studies on ground ULV application in which deposition was measured.
2. TTR_t (µg/cm^2) = [(Day 0 Residue from MS TTR study (µg/cm^2) x Application Rate (0.010 lb ai/A)) / Application Rate of MS TTR Study (3.83 lb ai/A))] * AgDISP Deposition Fraction
3. Dermal Dose (mg/kg/day) = [(TTR_t (µg/cm^2) * CF1 (0.001 mg/µg) * Transfer Coefficient (cm^2/hr - 180,000, adults; 49,000, children) * ET (1.5 hrs))] ÷ BW (kg)
4. MOE = PoD (mg/kg/day) ÷ Dose (mg/kg/day). See Table 5.3.3.3 for PODs.

Table 7.2.7. Residential Post-application Steady State Incidental Oral Exposure Estimates Resulting from Chlorpyrifos ULV Aerial Mosquitocide Application.

Application Parameters	Lifestage	Application Rate (mg ai)	Dermal Exposure (mg/day)[1]	Incidental Oral Dose (mg/kg/day)[2]	MOE[3]
1 mph Wind Speed Dv 0.5 = 60 µm 75 Foot Release Height	Children 1 to < 2 Years Old	0.010	0.028	$5.2x10^{-5}$	**3**
10 mph Wind Speed			0.0022	$4.5x10^{-6}$	**38**

Dv 0.5 = 40 µm 300 Foot Release Height					

1 Dermal exposure (mg/day) as calculated for children's aerial based ULV applications using the algorithms described in Table 6.2.4 above, and as described in Appendix C of the 2014 HHRA.
2 Incidental Oral Dose estimated using the algorithms as described below in Appendix C of the 2014 HHRA.
3 MOE = PoD (mg/kg/day) ÷ Dose (mg/kg/day). See Table 5.3.3.3 for PODs.

Table 7.2.8. Residential Post-application Steady State Incidental Oral Exposure Estimates Resulting from Chlorpyrifos ULV Ground Mosquitocide Application.

Lifestage	Application Rate (mg ai)	Dermal Exposure (mg/day)[1]	Incidental Oral Dose (mg/kg/day)[2]	MOE[3]
Children 1 to < 2 Years Old	0.010	0.0024	$4.5x10^{-6}$	**37**

1 Dermal exposure (mg/day) as calculated for children's ground based ULV applications using the algorithms described in Table 6.2.5 above, and as described below in Appendix C of the 2014 HHRA.
2 Incidental Oral Dose estimated using the algorithms as described in Appendix C of the 2014 HHRA.
3 MOE = PoD (mg/kg/day) ÷ Dose (mg/kg/day). See Table 5.3.3.3 for PODs.

7.3 Residential Risk Estimates for Use in Aggregate Assessment

All residential risks assessed with the updated PBPK-derived PODs are of concern (i.e., all MOEs are < the LOC of 100). Therefore, quantitatively aggregating residential exposures with food and drinking water exposures would also result in risks of concern.

8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast) employed for chlorpyrifos. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (*e.g.*, children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling coupled with methods employed for residential risk assessments for turf products.

In the 2011 occupational and residential exposure assessment, the potential risks to bystanders from spray drift and exposure from volatilization were identified as possible concerns. Spray drift is the movement of aerosols and volatile components away from the treated area during the application process. The potential risks from spray drift and the impact of potential risk reduction measures were assessed in July 2012 (J. Dawson *et al.*, D399483, 07/13/2012). This evaluation supplemented the 2011 assessment where limited monitoring data indicate risks to bystanders. To increase protection for children and other bystanders, chlorpyrifos technical registrants voluntarily agreed to lower application rates and to other spray drift mitigation measures (R. Keigwin, 2012). As of December 2012, spray drift mitigation measures and use restrictions appear on all chlorpyrifos agricultural product labels. For the 2014 HHRA, spray drift risks were updated due to the use of the PBPK-PD model which impacted the PoDs, and

thus spray drift risk estimates. This assessment updates chlorpyrifos risks once more to incorporate the approach applied for PBPK-derivation of PoDs for infants, children, and adults based on the exposures estimated from the indoor crack and crevice uses of chlorpyrifos during the time of the CCCEH cohort.

With a dermal and incidental oral LOC of 100, all non-occupational spray drift risk estimates are of concern at the field edge with the use of certain application rates, nozzle droplet sizes, and application methods. Buffer distances > 300 feet are needed for MOEs to be not of concern. The estimated buffer distances are in excess of those agreed to by the technical registrants in July 2012. All drift risk estimates are presented in Appendix C.

9.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

In January 2013, a preliminary assessment of the potential risks from volatilization was conducted (R. Bohaty *et al.*, D399484 and D400781, 01/31/2013). The assessment evaluated the potential risks to bystanders, or those who live and/or work in proximity to treated fields, from inhalation exposure to vapor phase chlorpyrifos and chlorpyrifos-oxon emitted from fields following application of chlorpyrifos. The results of the January 2013 assessment indicated that offsite concentrations of chlorpyrifos and chlorpyrifos-oxon may exceed the target concentration based on the toxicological endpoints used at that time (J. Hotchkiss *et al.,* EPA MRID 48139303).

In June 2014, a re-evaluation of the 2013 preliminary volatilization assessment was conducted since the Registrant had conducted and submitted two, high quality nose-only vapor phase AChE inhibition inhalation studies for both chlorpyrifos and chlorpyrifos-oxon (W. Irwin, D411959, 06/25/2014) to address the uncertainty surrounding exposure to aerosol versus vapor phase chlorpyrifos. In the vapor studies, female rats were administered a saturated vapor, meaning that the test subjects received the highest possible concentration of chlorpyrifos or chlorpyrifos-oxon which can saturate the air in a closed system. At these saturated concentrations, no statistically significant inhibition of AChE activity was measured in RBC, plasma, lung, or brain at any time after the six-hour exposure period in either study. Under actual field conditions, indications are that exposures to vapor phase chlorpyrifos and its oxon would be much lower as discussed in the January 2013 preliminary volatilization assessment. Since the studies demonstrated that no toxicity occurred even at the saturation concentration, the agency concluded that there was no risk potential, as risk is a function of both exposure and hazard.

However, in the current risk assessment for chlorpyrifos, the PoDs for risk assessment have been chosen to be protective of potential neurological effects below levels where AChE inhibition could occur. For that reason, a quantitative bystander/volatilization assessment has been included in this update. This assessment is an update to the 2013 assessment and has been updated to reflect air monitoring data collected since 2006, and the updated PoDs for chlorpyrifos.

There are six available chlorpyrifos air monitoring studies that were conducted since 2006 (brief study summaries available in W. Britton, D388165, 06/27/2011). These include:

- One application site study conducted in North Central and Yakima Valley, OR by the University of Washington Department of Environmental and Occupational Health Sciences, and
- Five ambient air studies
    - one conducted in North Central and Yakima Valley, by the University of Washington Department of Environmental and Occupational Health Sciences;
    - two conducted by Pesticide Action Network North America (PANNA) in Washington and Minnesota; and
    - two conducted by CalDPR.

Application site air monitoring refers to the collection of air samples around the edges of a treated field during and after a pesticide application. Samples are generally collected for short intervals (e.g., < 8 hours), for at least the first day or two after application with subsequent samples increasing in duration. In this type of study, it is typically known when an application occurred, the equipment used for the application, and the application rate. Application site monitoring data represents an exposure to vapors at or near the field edge resulting from an application.

Ambient air monitoring typically is focused on characterizing the airborne pesticide levels within a localized airshed or community structure of some definition (e.g., city, township, or municipality). This type of monitoring effort also can be focused on capturing chronic background levels or other temporal characteristics of interest such as focusing on seasonal pesticide use patterns. Typically, samples are taken for 24 consecutive hours and collected at the same site over an extended period of time (e.g., several weeks or months). In contrast to application site air monitoring, information on the precise timing and location of pesticide applications are rarely collected in ambient air monitoring studies. However, this does not mean that an application did not occur near an ambient sampler during the monitoring period

The EPA has assessed residential bystander exposure to chlorpyrifos based on the available ambient and application site air monitoring data (Tables 9.1 and 9.2). The chlorpyrifos bystander volatilization inhalation exposure assessment includes acute and steady state exposure scenarios. The acute scenario compares the maximum air concentration detected in the monitoring studies to the acute PoD. The steady state scenario compares the arithmetic mean chlorpyrifos air concentration from several monitoring studies to the steady state PoD.

The EPA has assessed residential bystander exposure from field volatilization of applied chlorpyrifos based on available *ambient* (five studies/11 locations) and *application site* (one study/2 locations) air monitoring data. For adults, of the 11 acute *ambient* air concentrations assessed, six resulted in risk estimates that are of concern (i.e., MOEs < 100). Only one steady state *ambient* air concentration resulted in a risk estimate not of concern (i.e., MOEs > 100). For the *application site* air concentrations assessed, all resulted in risk estimates of concern (i.e., MOEs < 100). For children 1 to <2 years old, of the 11 acute *ambient* air concentrations assessed, all resulted in risk estimates that are of concern (i.e., MOEs < 100). Only four steady state *ambient* air concentration resulted in a risk estimate not of concern (i.e., MOEs > 100). For the *application site* air concentrations assessed, all resulted in risk estimates of concern (i.e.,

MOEs < 100). All bystander risk estimates are presented in Appendix D.

Table 9.1. Chlorpyrifos Preliminary Volatilization Risk Analysis for Residential Adult Bystanders.					
Study, Year	**Sampler/ Site Location**	**Maximum Air Concentration (ng/m^3)**	**Arithmetic Mean Air Concentration (ng/m^3)**	**Acute MOEs[1] (LOC = 100)**	**Steady State MOEs[2] (LOC = 100)**
Application Site Data					
WA DOH, 2008	North Central District Perimeter Site	1145	153	**3.5**	**1.4**
	Yakima Valley Perimeter Site	1002	294	**4**	**0.71**
Ambient Air Data					
WA DOH, 2008	North Central District Ambient	21	7	190	**31**
	North Central District Receptor	606.8	33	**6.6**	**6.4**
	Yakima Valley Ambient	30	9	130	**23**
	Yakima Valley Receptor	243	30	**16**	**6.9**
Parlier, CA (CalDPR) 2009		150	96	**27**	**2.2**
Cowiche PANNA 2006		462	155	**8.7**	**1.4**
PANNA MN Drift Study (2006-2009)	Browerville Site B	15	2.7	270	**79**
	Perham Site C	47	1.9	**85**	110
CDPR 2014 Air Monitoring Network	Salinas, CA	14.1	5.4	280	**39**
	Shafter, CA	337.9	92.1	**12**	**2.3**
	Ripon, CA	14.1	14.1	280	**15**

1 Acute MOE = Acute PoD (4,000 ng/m^3) / Study maximum air concentration (ng/m^3).
2 Steady State MOE = Steady State PoD (210 ng/m^3) / Study arithmetic mean air concentration (ng/m^3).

Table 9.2. Chlorpyrifos Preliminary Volatilization Risk Analysis for Residential Children (1 to <2 Years Old) Bystanders.					
Study, Year	**Sampler/ Site Location**	**Maximum Air Concentration (ng/m^3)**	**Arithmetic Mean Air Concentration (ng/m^3)**	**Acute MOEs[1] (LOC = 100)**	**Steady State MOEs[2] (LOC = 100)**
Application Site Data					
WA DOH, 2008	North Central District Perimeter Site	1145	153	**1.1**	**4.4**
	Yakima Valley Perimeter Site	1002	294	**1.3**	**2.3**
Ambient Air Data					
WA DOH, 2008	North Central District Ambient	21	7	**62**	100
	North Central District Receptor	606.8	33	**2.1**	**21**
	Yakima Valley Ambient	30	9	**43**	**73**
	Yakima Valley Receptor	243	30	**5.3**	**22**

Table 9.2. Chlorpyrifos Preliminary Volatilization Risk Analysis for Residential Children (1 to <2 Years Old) Bystanders.					
Study, Year	**Sampler/ Site Location**	**Maximum Air Concentration (ng/m^3)**	**Arithmetic Mean Air Concentration (ng/m^3)**	**Acute MOEs[1] (LOC = 100)**	**Steady State MOEs[2] (LOC = 100)**
Parlier, CA (CalDPR) 2009		150	96	**8.7**	**7.1**
Cowiche PANNA 2006		462	155	**2.8**	**4.4**
PANNA MN Drift Study (2006-2009)	Browerville Site B	15	2.7	**87**	260
	Perham Site C	47	1.9	**28**	350
CDPR 2014 Air Monitoring Network	Salinas, CA	14.1	5.4	**92**	130
	Shafter, CA	337.9	92.1	**3.8**	**7.4**
	Ripon, CA	14.1	14.1	**92**	**48**

1 Acute MOE = Acute PoD (1,300 ng/m^3) / Study maximum air concentration (ng/m^3).
2 Steady State MOE = Steady State PoD (680 ng/m^3) / Study arithmetic mean air concentration (ng/m^3).

Characterization of Bystander Risk Assessment/Uncertainties

Some of the limitations and considerations that have been identified that should be considered in the interpretation of these results include:

- Most of the data utilized in this preliminary assessment are 24-hour air samples. When these data are used, an assumption is made that an individual is exposed to the same air concentration for 24-hours every day. However, this is not always the case as real world time-activity data indicate that many parts of the population move from site to site on a daily basis (e.g., go to work and back).

- This assessment is only representative of outdoor concentrations (i.e., the exposure and risk estimates assume an individual is outdoors all the time). It does not take into account potential effects of air conditioning systems and similar air filtration systems which could potentially reduce air concentrations indoors. The agency believes that indoor concentrations will be at worst equivalent to outdoor concentrations and may potentially be lower.

- All of the data used for this analysis have been generated in California and Washington; however, chlorpyrifos is used in many regions throughout the country. Therefore, the results based on the limited available air monitoring data were used to represent the rest of the country due to a lack of adequate information for any other region. It is unclear what potential impacts this extrapolation might have on the risk assessment. Factors such as meteorology and cultural practices may impact the overall amounts of chlorpyrifos that volatilize from a treated field as well as the rate at which it volatilizes.

- As part of the December 2009 SAP, the agency presented their analysis of several models that could be used as screening tools to predict the air concentration and volatilization flux based on intrinsic properties and transport behaviors of pesticides. These models would allow the agency to better represent the potential volatilization of semi-volatile

pesticides across various regions of the country and thus would provide refinement to this assessment over using straight air monitoring data. The SAP provided a number of comments regarding the agency's model analysis, including the recommendation to evaluate some additional models. The agency is currently in the process of evaluating the SAP's comments. As appropriate, the agency will revise the modeling approach presented to the SAP for determining the rate of volatilization (flux) for semi-volatile pesticides and for estimating air concentrations of applied pesticides in the atmosphere under varying environmental conditions. After any policies or procedures are put into place, the agency may revisit the residential bystander exposure and risk assessment.

10.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard, or the risks themselves can be aggregated. The steady state aggregate assessment includes food, drinking water, and residential exposures.

For chlorpyrifos aggregate assessment, a DWLOC approach is used to calculate the amount of exposure available in the total 'risk cup' for chlorpyrifos in drinking water after accounting for any chloropyrifos exposures from food and residential uses. This DWLOC is then compared to the EDWC to determine if there is an aggregate risk of concern. However, because the dietary risks from food exposure alone and from residential exposure alone are of concern, it is not possible to calculate a DWLOC; essentially, the steady state aggregate DWLOC is '0' after accounting for food and residential exposures.

[See the December 2014 chlorpyrifos HHRA for details of the DWLOC approach and calculations. See the April 2016 DWA for the EDWCs.]

11.0 Occupational Exposure and Risk Estimates

HED had previously conducted both steady state occupational handler and post-application exposure analyses for chlorpyrifos (W. Britton, D424484, 12/29/2014). However, occupational exposures and risks have been updated to incorporate the approach applied for PBPK-derivation of PoDs for infants, children, and adults based on the exposures estimated from the indoor crack and crevice uses of chlorpyrifos during the time of the CCCEH cohort. The scenarios, assumptions, and exposure inputs have not changed since the previous assessment; the assessment below estimates occupational handler exposures using the updated PBPK-derived steady state PoDs. Details on the exposure inputs, scenarios, and assumptions can be found in the 2014 ORE assessment (W. Britton, D424484, 12/29/2014).

It is agency policy to use the best available data to assess exposure. The same chemical-specific dislodgeable foliar residue (DFR) studies were used for the 2014 assessment of occupational post-application exposure to chlorpyrifos have been used for this update, including: emulsifiable concentrate formulations on sugarbeets, pecans, citrus, sweet corn, cotton, and turf; wettable powder formulations on almonds, apples, pecans, cauliflower, tomato and turf; granular

formulations on sweet corn and turf; a total release aerosol formulation on ornamentals; and a microencapsulated liquid formulation on ornamentals.

Several sources of generic data were used in this assessment as surrogate data including: Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; the Outdoor Residential Exposure Task Force (ORETF) database; the Agricultural Reentry Task Force (ARTF) database; ExpoSAC Policy 14 [Standard Operating Procedures (SOPs) for Seed Treatment]; HED's 2012 Residential SOPs for Residential Pesticide Exposure Assessment: Lawns/Turf, Outdoor Fogging/Misting Systems, registrant-submitted exposure monitoring studies MRIDs 44180401, 44301301, 44793301, 44829601, 42974501, 43062701, 44748101, 44748102, 46722701, and 46722702, and published literature studies. Some of these data are proprietary, and subject to the data protection provisions of the *Federal Insecticide, Fungicide, and Rodenticide Act (*FIFRA).

In the 2011 HHRA (D. Drew *et al.*, D388070, 06/30/2011), additional studies were recommended to address uncertainties regarding the formation of chlorpyrifos oxon and its decay following applications in greenhouses. To date, no additional data have been submitted.

11.1 Steady State Occupational Handler Risk

The term handlers is used to describe those individuals who are involved in the pesticide application process. There are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of a chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event. Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from chlorpyrifos use. For purpose of occupational handler assessment, the parent chlorpyrifos is the relevant compound.

Current labels generally require that handlers use normal work clothing (i.e., long sleeved shirt and pants, shoes and socks) and coveralls, chemical resistant gloves, and dust/mist respirators. Also, some products are marketed in engineering controls such as water soluble packets. In order to determine what level of personal protection is required to alleviate risk concerns and to ascertain if label modifications are needed, steady state exposure and risk estimates were updated for occupational handlers of chlorpyrifos for a variety of scenarios at differing levels of personal protection including engineering controls.

The occupational handler scenarios, assumptions, and exposure inputs have not changed since the previous assessment.

<u>Summary of Occupational Handler Non-Cancer Exposures and Risk Estimates</u>
Using the updated PBPK-derived steady state PODs and uncertainty factors (dermal and inhalation LOC = 100), all agricultural occupational handler scenarios, all primary seed treatment handler scenarios, and all secondary seed treatment (planter) scenarios are of concern with label-specified and maximum levels of personal protective equipment (PPE) or engineering

controls (MOEs < 100). Detailed result tables are provided in Appendix E.

11.2 Steady State Occupational Post-Application Risk Estimates

HED uses the term, post-application, to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as reentry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure. Chlorpyrifos parent compound is the residue of concern for occupational post-application dermal exposures; however, it may be possible that the formation of the oxon is greater and its deactivation slower in greenhouses when compared to the outdoor environment and that an assessment may be needed for exposure to the oxon in greenhouse settings.

11.2.1 Occupational Post-application Inhalation Exposure/Risk Estimates

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. Previously, a quantitative post-application inhalation risk assessment was not conducted for chlorpyrifos or chlorpyrifos oxon due to the lack of toxicity seen in the available nose-only vapor phase AChE inhibition inhalation studies (W. Britton, D424484, 12/29/2014). The studies did not demonstrate inhalation toxicity, or inhibition of AChE activity measured in RBC, plasma, the lungs, and the brain following exposure to chlorpyrifos or chlorpyrifos oxon vapor, even at the saturation concentration. However, since the previous assessment, the PODs have been updated to reflect the PBPK-derived steady state PoD based on a TWA of blood concentrations corresponding to levels likely to have occurred in the CCCEH cohort, as discussed in Section 5.3.3. Therefore, the agency will be assessing occupational post-application inhalation from the registered uses of chlorpyrifos.

The agency has sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/document?D=EPA-HQ-OPP-2014-0219-0001). During Registration Review, the agency will utilize this analysis, and take into consideration the risks identified from the residential bystander assessment, to determine if data (i.e., flux studies) or further analysis is required for chlorpyrifos.

In addition, the agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the agency will continue to identify the need for and, subsequently, the way to incorporate

occupational post-application inhalation exposure into the agency's risk assessments.

The Worker Protection Standard for Agricultural Pesticides contains requirements for protecting workers from inhalation exposures during and after greenhouse applications through the use of ventilation requirements.[40 CFR 170.110, (3) (Restrictions associated with pesticide applications)].

11.2.2 Occupational Post-application Dermal Exposure/Risk Estimates

Occupational post-application assessments were previously performed for: 1) exposures to the parent compound chlorpyrifos in outdoor environments (uses other than greenhouse), 2) exposures to the parent chlorpyrifos (only) in greenhouses and 3) exposures to both the parent and the oxon metabolite in greenhouses; and incorporated: 1) a PBPK modeled dermal PoD specific for occupational assessment 2) the updated master use summary document, 3) the updated adult (female) default body weight, and 4) the changes relating to agricultural transfer coefficients (TC) as described in the *Science Advisory Council for Exposure (ExpoSAC) Policy 3 – Revised March 2013*[17] (W. Britton, D424484, 12/29/2014).

However, the steady state PODs and uncertainty factors have changed since the previous assessment. Therefore, the occupational post-application exposure assessment has been revised. The scenarios, assumptions, and exposure inputs have not changed since the previous assessment; the assessment below estimates occupational post-application dermal exposures using the updated PBPK-derived steady state PODs. Details on the exposure inputs, scenarios, and assumptions can be found in W. Britton, D424484, 12/29/2014. Detailed result tables are provided in Appendix F.

Summary of Occupational Post-application Non-Cancer Exposures and Risk Estimates
263 total occupational post-application scenarios were evaluated. The restricted entry intervals (REIs) on the registered chlorpyrifos labels range from 24 hours to 5 days. All scenarios were of concern on Day 0 with a dermal LOC of 100. On average, scenarios were not of concern $\geq$ 18 days after treatment.

[17] http://www.epa.gov/opp00001/science/exposac-policy-3-march2013.pdf

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13.0 List of Appendices

Appendix A: Non-occupational exposure estimates following mosquitocide applications
Appendix B: Residential (golfing) post-application exposure estimates
Appendix C: Non-occupational spray drift exposure and risk estimates
Appendix D: Non-occupational bystander post-application inhalation exposure and risk estimates
Appendix E: Occupational handler exposure and risk estimates
Appendix F: Occupational post-application dermal exposure and risk estimates

American Agriculture Speaks Out in Support of Chlorpyrifos

(Jan 16, 2017)

The attached petitions with **2300** signatures in support of chlorpyrifos, represent American growers, farmers and others from across the U.S. who are involved in producing the food American consumers rely on and the crops that are important exports supporting U.S. trade. Signees have a simple, common message to EPA:

We ask you, the US EPA to retain the current crop tolerances and the continued registration and availability of use of the chlorpyrifos-containing products we need.

Those involved with production of citrus, corn &soybean, cotton, wheat and sugar beets have petitions specific to their crop so they could emphasize the critical importance of chlorpyrifos to their operations. Crop-specific petitions were signed by;

199 for citrus

619 for corn & soybean

187 for cotton

399 for wheat

224 for sugar beets

For other crops, **672,** representing the full range of crops on labels for chlorpyrifos products, signed the petition.

Petitions were signed during EPA's public comment period for EPA's Chlorpyrifos: Tolerance Revocations; Notice of Data Availability and Request [EPA-HQ-2015-0653] from November 17, 2016 to January 16, 2017.Signatures were collected by Dow AgroSciences and are being submitted by Dow AgroSciences with the understanding and agreement of those who signed the petitions.

Submitted on January 16, 2017 by:

Dow AgroSciences, LLC
9330 Zionsville Rd
Indianapolis, IN 46268

Chlorpyrifos is a critical tool for American crop production

In the United States, growers of more than 50 different types of crops, including cereal, oil, forage, fruit, nut and vegetable crops count on chlorpyrifos as a critical tool. Farmers rely on chlorpyrifos because of its efficacy, broad-spectrum control, low cost, and tank mix compatibility. For many important pests, growers face limited or no viable alternatives to chlorpyrifos. And, when an outbreak of a new pest occurs, growers look to chlorpyrifos as a proven first-line of defense. Growers also look to chlorpyrifos for the ease of implementation into existing Integrated Pest Management and Integrated Resistance Management programs, and the minimal impact on beneficial insects compared to alternative chemistries.

We ask you, the US EPA to retain the current crop tolerances and the continued registration and availability of use of the chlorpyrifos-containing products we need.

First Name	Last Name	State	Yes I have read and understand that this petition will be submitted into official public comment dockets and any personal information included may be publicly viewable Indicate yes by checking here
Manfred	Schosnig	OR	1
KENNETH	TAMURA	IDAHO	1
Jimmy	Wood	Ga.	1
mark	hawke	GA	1
Don	Tolmie	Idaho	1
Katherine	Blanchard	WA	1
Joe	Weitz	ID	1
Leland	Tiegs	Idaho	1
Matthew	Ray	GA	1
Keith	Kubik	California	1
Gary	Lucas	Idaho	1
Gene	Schmitt	Idaho	1
Leslie	Dean	ID	1
Richard	Matteson	North Dakota	1
Justin	Lynch	Washington	1
Kevin	Marshall	Oregon	1
Sidney	Naito	ID	1
Grady	Whiddon	Ga	1
Matthew	Hamilton	OR	1
Austin	Purvis	Georgia	1

Talley	Brim	Ga	1
Joel	Horn	CO	1
Harold	Mckay	Oregon	1
Josh	White	GA	1
Darin	Garland	GA	1
Donna	Cowart	GA	1
Matt	Taylor	GA	1
Chase	Floyd	GA	1
Willie	Wiggins	GA	1
Jimmy	Wiggins	GA	1
Greg	Howard	Ga	1
Jeffrey	Howard	GA	1
Lamar	White	GA	1
Rebecca	White	GA	1
McKinley	White	GA	1
June	Howard	GA	1
Aaron	Wolff	KS	1
Kenneth	Tucker	KS	1
Michael	Bahr	Kansas	1
Cole	McCurry	KS	1
Ryan	Mcbride	Oklahoma	1
Shawn	Thornton	Ks	1
Travis	Kolm	Kansas	1
Keith	Hulteen	Colorado	1
Brett	Despain	Idaho	1
Julie	Gordon	MI	1
Brent	Sutton	DE	1
russell	byerley	washington	1
Josh	Prow	WA	1
Kevin	Schwertfeger	Kansas	1
Timothy	Guttridge	OREGON	1
Thomas	Egan	Oregon	1
jeff	Newton	Oregon	1
Justin	Jones	Georgia	1
Matt	Storlie	Idaho	1
Willis	Connell	NC	1
Tim	Semler	ND	1
shawn	knudson	north dakota	1
JP Tom	Bodderij	Arizona	1
Jason	Richter	North Dakota	1
Wayne	Christ	North Dakota	1
Ben	Lee	ND	1
Andy	Grundstad	North Dakota	1
William	McMullin	UT	1

Chlorpyrifos is a critical tool for American citrus producers

Chlorpyrifos products are especially critical for use in citrus to control damaging insect pests and maintain the highest standards of quality and maximize yields. In citrus, chlorpyrifos is less disruptive to beneficial insects than alternative chemistries, a good rotational partner, and exports are supported by international tolerances/residue limits that are in place. Chlorpyrifos is widely used in citrus. It is effective in treating a number of insect pests including scale, katydids, mites, thrips, leaf miner and Asian citrus psyllid depending on the growing region. For example, in California infestations California Red Scale can get out of control quickly making control critical. While other products may offer control, unlike chlorpyrifos, their use is outside the timing for Scale control and so repeated use is needed in a grove, which increases the chance of resistance developing. Chlorpyrifos is also crucial in California for the control of ants, which enables natural enemies to keep the majority of insect pests in check. In Florida, citrus crops are currently being treated up to eight times per year with insecticides to reduce Asian citrus psyllid. Chlorpyrifos is primarily used to control the Asian citrus psyllid, which is the vector of the bacteria that causes citrus greening. Without chlorpyrifos, fresh oranges and orange juice availability could be hampered.

We ask you, the US EPA to retain the current tolerances for citrus and the continued registration and availability of use of the chlorpyrifos-containing products we need.

First Name	Last Name	State	Yes I have read and understand that this petition will be submitted into official public comment dockets and any personal information included may be publicly viewable Indicate yes by checking 1
Mary	Porter	Georgia	1
Chris	Pickering	Georgia	1
Clay	Croft	KS	1
Travis	Kolm	Kansas	1
Cole	McCurry	KS	1
JP Tom	Bodderij	Arizona	1
Emma	Vavricka	NE	1
Sarah	Cassel	North Dakota	1
CARLY	WALKER	NE	1
Neal	Braswell	GA	1
Terry	Turner	Ga	1

Chlorpyrifos is a critical tool for American corn and soybean growers

Chlorpyrifos is a critical tool for American corn and soybean growers. For corn, it is effective in treating a number of insect pests due to its broad spectrum control, fast knockdown, and action on foliar-feeding and soil-dwelling insects. In soybeans, growers also rely on chlorpyrifos for broad spectrum insect control, fast knockdown of insect pests, and strong support database on health and ecological safety. The number one pest in soybeans in the Midwest and Plains is the soybean aphid. In 2014 alone, chlorpyrifos was used on over half of the soybean acres treated for aphids. For both crops, chlorpyrifos is less disruptive to beneficial insects than alternative chemistries and is also an important tool for IRM programs helping to provide a "tool-box" of options for sustainable control programs.

We ask you, the US EPA to retain the current tolerances for corn and soybeans and the continued registration and availability of use of the chlorpyrifos-containing products we need.

First Name	Last Name	State	Yes I have read and understand that this petition will be submitted into official public comment dockets and any personal information included may be publicly viewable Indicate yes by checking here
Ry	McRee	Georgia	1
kenneth	tamura	idaho	1
Wood	Jimmy	Ga.	1
Jimmy	Wood	Ga	1
Dale	Weeks	NC	1
Wallace	Sholar	Ga	1
Mary	Porter	Georgia	1
Henry	Kallal	Illinois	1
Chris	Pickering	Georgia	1
Brian	Beckley	ND	1
Brett	Schroeder	ND	1
george	crookham	Idaho	1
Joey	Gonsalves	CA	1
Justin	Wieskamp	NE	1
Brian	Mattingly	Indiana	1
Roger	Sievers	Idaho	1
Alex	Fornshell	ND	1
Aaron	Wolff	Ks	1
Marc	Johnson	Kansas	1
Michael	Bahr	Ks	1
Dylan	Shotton	Ks	1
Cole	McCurry	KS	1
Steve	Deters	Kansas	1

Chlorpyrifos is a critical tool for American cotton producers

American cotton producers need chlorpyrifos. It is effective in treating a number of insect pests including Lygus bug, plant bug, stink bug, silverleaf whitefly and aphids, as well as, other economically important insect pests such as spider mites, armyworm and soybean looper due to its fast knockdown of insect pests and broad spectrum control. Chlorpyrifos is especially needed for aphid and whitefly control since these pests produce large amounts of honeydew which makes the cotton lint difficult to gin. Gins will discount and may even reject the impacted crop. Chlorpyrifos is also needed as a rotational partner in IRM programs to ensure growers have a “tool-box” of effective control options.

We ask you, the US EPA to retain the current tolerances for cotton and the continued registration and availability of use of the chlorpyrifos-containing products we need.

First Name	Last Name	State	Yes I have read and understand that this petition will be submitted into official public comment dockets and any personal information included may be publicly viewable Indicate yes by checking 1
Jimmy	Wood	Ga.	1
Kyle	Shedd	Georgia	1
Michael	Bloodworth	Georgia	1
Wallace	Sholar	Ga	1
Jim	Dunlap	Georgia	1
Mary	Porter	Georgia	1
Chris	Pickering	Georgia	1
Austin	Purvis	Georgia	1
Tyler	Hendley	Ga	1
Travis	Kolm	Kansas	1
Cole	McCurry	KS	1
Ryan	Mcbride	Oklahoma	1
Weldon	Gilleland	texas	1
bradley	gemblet	tx	1
LeAnn	Bruns	IN	1
Dietrich	Gembler III	Texas	1
Emma	Vavricka	NE	1
Nicholas	Martin	KS	1
David	George	SC	1
MANDEL	MULLIS	GA	1
Neal	Braswell	GA	1
Jay	Hendley	Georgia	1

Terry	Turner	Ga	1
Lily	Hyman	NC	1
Ross	Greene	GA	1
bob	joerger	nd	1
Chad	Bladow	North Dakota	1
James	Freeman	Georgia	1
Crystal	Gaillard	Georgia	1
Harold	Cochran	Wa	1
Michael	Davis	South Carolina	1
James	Mueller	CA	1
Samantha	Petersen	South Dakota	1
Tyler	Nabors	Oklahoma	1
louie	johnson	north carolina	1
Dan	Bouck	IN	1
Kevin	Sheaffer	IN	1
Christopher	Voglewede	Indiana	1
george	fort	indiana	1
Di	Conger	IN	1
Jillian	Schmiedt	IN	1
Robert	Byrne	South Carolina	1
Linda	Clark	IN	1
Alistair	McKay	CA	1
abe	smith	nebraska	1
Haley	Nabors	OK	1
Leigh	Muir	Indiana	1
Chad	Shivar	NC	1
Nick	Higgins	California	1
jeff	bost	arkansas	1
Jason	Worthington	MO	1
Cameron	Horine	Missouri	1
JEREMY	SHEFFER	ARKANSAS	1
Benjamin	Olson	Hawaii	1
Kellar	Becker	Missouri	1
Aaron	Wade	Nc	1
Rance	Wekborn	Al	1
Deanna	Smith	MO	1
Elijah	adams	texas	1
Jay	Golz	MS	1
James	Allen	NC	1
Bruce	Niederhauser	NC	1
Trent	Brusseau	Idaho	1
Jace	Householder	Az	1
Clayton	Houchin	California	1
Philip	Shewmaker	Idaho	1

Chlorpyrifos is a critical tool for American wheat producers

American wheat producers count on chlorpyrifos because of its broad spectrum insect control, fast knockdown of insect pests, strong support database on health and ecological safety, and efficacy. For several important pests, growers have limited or no viable alternatives. Aphids are the most troublesome insect pests in wheat in the United States, and can inflict substantial losses. Chlorpyrifos provides fast knockdown of aphids and is the only active ingredient that can effectively control Russian wheat aphid after they are protected inside of rolled-up wheat leaves in later colonization stages. As the leading insecticide in wheat midge control and the second leading insecticide active ingredient in aphid control, the use of chlorpyrifos is crucial to U.S. wheat production. Chlorpyrifos is also an important rotational partner in IRM programs, helping to ensure growers have a “tool-box” of options for sustainable control programs.

We ask you, the US EPA to retain the current tolerances for wheat and the continued registration and availability of use of the chlorpyrifos-containing products we need.

First Name	Last Name	State	Yes I have read and understand that this petition will be submitted into official public comment dockets and any personal information included may be publicly viewable Indicate yes by checking 1
Jimmy	Wood	Ga	1
Wallace	Sholar	Ga	1
Mary	Porter	Georgia	1
Chris	Pickering	Georgia	1
Sidney	Naito	ID	1
Joey	Gonsalves	CA	1

Chlorpyrifos is a critical tool for American sugar beet growers

Chlorpyrifos products are essential for use in sugar beets. Chlorpyrifos is one of the most used active ingredients to control pests in sugar beets and has been an integral component in sugar beet pest management programs for decades due to its efficacy, and broad spectrum pest control using conventional agricultural application equipment. For several important pests, growers have limited or no viable alternatives. Maintaining the availability of chlorpyrifos in sugar beets is important for the effective control of insect pests and the viability of long-term resistance management programs.

We ask you, the US EPA to retain the current tolerances for sugar beets and the continued registration and availability of use of the chlorpyrifos-containing products we need.

First Name	Last Name	State	Yes I have read and understand that this petition will be submitted into official public comment dockets and any personal information included may be publicly viewable Indicate yes by checking here
KENNETH	TAMURA	IDAHO	1
Leland	Tiegs	ID	1
Mary	Porter	Georgia	1
Chris	Pickering	Georgia	1
Sidney	Naito	ID	1
Bill	Haun	Idaho	1
Cole	McCurry	KS	1
Travis	Kolm	Kansas	1

LeAnn	Bruns	IN	1
Emma	Vavricka	NE	1
Brock	Leonard	WA	1
Cleo	Miller	Idaho	1
Sarah	Cassel	North Dakota	1
CARLY	WALKER	NE	1
Paul	Pfenninger	Michigan	1
Clay	Altepeter	MN	1
David	Dahlsad	North Dakota	1
Lily	Hyman	NC	1
Bob	Joerger	ND	1
Pete	Chwialkowski	MN	1
Brock	Larson	Minnesota	1
Justin	Krieg	North Dakota	1
Kevin	Anderson	Minnesota	1
jon	wurden	mn	1
Chad	Bladow	North Dakota	1
Joel	Gasper	MN	1

Dow AgroSciences LLC's Comments on 2016 Notice of Data Availability, Revised Human Health Risk Assessment and Refined Drinking Water Assessment for Chlorpyrifos

(EPA Docket: EPA-HQ-OPP-2015-0653)

AUTHOR(S)

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STUDY COMPLETED ON

January 17, 2017

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I. Introduction

Dow AgroSciences LLC ("DAS") respectfully submits these comments on the Chlorpyrifos: Tolerance Revocations; Notice of Data Availability and Request for Comment (EPA-HQ-OPP-2015-0653-0402), published in the Federal Register, 18 Fed. Reg. 81,049 (Nov. 17, 2016), and accompanying assessments including, specifically, the Chlorpyrifos Revised Human Health Risk Assessment for Registration Review (the "2016 RHHRA"), EPA-HQ-OPP-2015-0653-0454 (Nov. 3, 2016), and the Chlorpyrifos Drinking Water Assessment for Registration Review, EPA-HQ-OPP-2015-0653-0437 (Apr. 14, 2016). In addition to the information submitted here, DAS incorporates by reference and seeks Agency review of all prior DAS comments and other submissions as listed in Appendix A.

A. Background on Chlorpyrifos

Chlorpyrifos is an organophosphorus ("OP") insecticide first registered in the United States in 1965. Products containing chlorpyrifos protect more than fifty valuable U.S. food crops from destruction due to a variety of insect pests. Key crop uses include citrus fruits, corn, cotton, soybeans, sugarbeets, and wheat. Chlorpyrifos is one of the most widely used insecticides in the world, with approved uses in approximately 100 countries. The sustained importance of chlorpyrifos for global insect pest management is due to its outstanding efficacy and favorable environmental and human health characteristics. Revocation of chlorpyrifos tolerances would have severe negative economic impacts on American agriculture and global trade and therefore should be considered a significant regulatory action.

Chlorpyrifos is highly effective in controlling a broad spectrum of both foliar-feeding and soil-dwelling insect pests, and its important role in resistance management and integrated pest management ("IPM") programs is widely recognized. The widespread international registration approvals for chlorpyrifos and establishment by the Codex Alimentarius Commission of more than fifty international maximum residue limits ("MRLs") for chlorpyrifos residues on food crop commodities have facilitated global free trade of treated crops.

Chlorpyrifos exhibits moderate mammalian toxicity (WHO Hazard Class II) and is not carcinogenic, a selective reproductive or developmental toxicant, or an endocrine disruptor. Inhibition of blood cholinesterase has been used by EPA as a protective regulatory health

endpoint, or point of departure ("PoD"), for risk assessment for over forty-five years.[1] Use of this endpoint was recently confirmed by the European Food Safety Authority ("EFSA") and also remains the gold standard and point of departure used by the World Health Organization and virtually all major global regulatory authorities.

Chlorpyrifos is biodegradable and has only short-to-moderate persistence in most environmental settings. In terrestrial ecosystems, chlorpyrifos rapidly dissipates from plant foliage (half-lives of <1–7 days). Soil surface half-lives are typically on the order of a few days to two weeks, whereas subsurface chlorpyrifos may demonstrate dissipation half-lives of one to two months. In aquatic ecosystems, chlorpyrifos dissipates very rapidly (half-life <24 hours) from the water column, and dissipation from sediments is similar to that observed for soils.

B. Regulatory History

In 2006, chlorpyrifos successfully completed EPA's Reregistration program under the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA") and the Federal Food, Drug, and Cosmetic Act ("FFDCA").[2] Reregistration was a comprehensive review of the human health and ecological effects of pesticide products that ensured that they met current scientific and regulatory standards and addressed any potential concerns that might have been raised by new research since the previous regulatory review. As a result of Reregistration, EPA determined that chlorpyrifos continued to meet strict safety standards, and all existing agricultural uses were reauthorized. Reregistration is followed every fifteen years by Registration Review of pesticide products pursuant to FIFRA in order to maintain confidence over the long run that the products continue to meet current standards.

In 2007, the Pesticide Action Network of North America and the Natural Resources Defense Council filed a petition with the Agency seeking to revoke tolerances and cancel the EPA registrations for chlorpyrifos (the "Petition").[3] The Petition was based in significant part on

[1] A point of departure is a dose estimate developed from experimental or observational data on a particular health effect.

[2] EPA regulates pesticides under a comprehensive, science-based regime pursuant to its authority under FIFRA and FFDCA.

[3] Under Section 408 of the FFDCA, as amended by the Food Quality Protection Act ("FQPA"), before a pesticide may be used on any food crop, EPA specifies the maximum amount of pesticidal residue (called a "tolerance") that may legally remain in or on foods. *See* 21 U.S.C.

a taxpayer-funded epidemiology study conducted by researchers at Columbia University (the "Columbia study") and first published in 2002. The Columbia study associated *de minimis* amounts of chlorpyrifos allegedly found in the umbilical cord blood of a group of mothers almost twenty years ago with neurodevelopmental effects allegedly found in their children later in life. In response to the Petition, EPA initiated the Registration Review of chlorpyrifos—even though the Agency was not statutorily required to complete another review of chlorpyrifos until 2022. As part of Registration Review, EPA conducted multiple risk assessments and convened several sessions of its FIFRA Scientific Advisory Panel ("SAP") to evaluate the Columbia study and other epidemiology studies as well as the Agency's draft framework for integrating epidemiology in risk assessment. The SAPs expressed significant concerns about the quantitative use of the Columbia study in risk assessment. Overall, the reports from these SAP meetings do not support the position that the Columbia study justifies disregarding over forty years of toxicological data that demonstrate the adequacy and protectiveness of the current regulatory standard.

Still not satisfied with EPA's efforts, the petitioners asked the U.S. Court of Appeals for the Ninth Circuit to force EPA to make a decision on the Petition. During these proceedings, EPA notified the court in March 2015 that it intended to deny the Petition, confirming the Agency's confidence in the current regulatory standard for chlorpyrifos and the rigorous toxicology data supporting that standard.[4]

EPA then abruptly changed course and advised the court in June 2015 that it intended to *grant* the petition by seeking revocation of all tolerances, citing purported drinking water exposure concerns (not even raised in the Petition) that the Agency was working to address. The court granted the petitioners' request and has set March 31, 2017, as the final deadline for EPA to make a decision on the Petition.

Instead of completing Registration Review, EPA issued a proposed rule on November 6, 2015, to revoke all tolerances previously established for food uses of chlorpyrifos, 80 Fed. Reg. 69,087 (Nov. 6, 2015) (the "Proposed Rule"). EPA's proposed revocation of tolerances would

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§346a. Without the requisite food safety tolerances, EPA would be required to cancel the underlying registrations for those uses.

[4] Status Rep., *In re Pesticide Action Network N. Am. v. U.S. EPA,* No. 14-72794 at 2 (9th Cir. Mar. 31, 2015), ECF No. 14 at 2.

effectively end most chlorpyrifos uses, including current uses on all crops in U.S. agriculture. The Proposed Rule was based, in part, on the Agency's admittedly incomplete drinking water assessment and, in part, on the Columbia study. Despite repeated requests, and the fact that the Columbia study was federally funded, the researchers have refused to make the full raw dataset from the study available for review and validation.

Undeterred by the prior SAPs' admonitions, the Agency went back to the SAP in the spring of 2016 with a proposal for a new regulatory standard for chlorpyrifos based directly on cord blood concentrations reported in the Columbia study. But the 2016 SAP rejected EPA's approach, deeming the Columbia study insufficient for quantitative use in risk assessment, citing numerous deficiencies in the study (including as to the validity and reliability of the reported test results), and expressing concerns with EPA's reliance on the study in the absence of the raw data. While the Agency maintained that being published in scientific journals was adequate validation of the Columbia study, the SAP countered that such peer review cannot be equated to a study conducted under Good Laboratory Practices ("GLPs"), which is a required condition of studies by registrants, especially when measurements and conclusions have not been independently replicated. The SAP was especially concerned about the "immense ramifications" that EPA's proposed deficient approach would have on U.S. agriculture. Not surprisingly, many of these concerns echoed the criticisms of the prior SAPs.

The shift to a reliance on the Columbia study to set a PoD did not reflect the emergence of new information. Columbia researchers started publishing in 2002 on exposure, with the infant outcome studies first appearing in 2004. EPA was therefore aware of the Columbia study results when it reaffirmed the current PoD based on cholinesterase inhibition as the appropriate and protective PoD several times, including as recently as December 2014. SAPs convened during that time period also supported the continued use of cholinesterase inhibition as the PoD.

In its current RHHRA, EPA is now advancing yet another new regulatory standard that hypothesizes (without factual support) as to how subjects in the Columbia study may have been exposed to just the right amount of chlorpyrifos in their homes to have resulted in the very low doses that allegedly caused neurodevelopmental effects that just a few months ago the Agency was attempting to support by reference to the cord blood data. But the SAP's conclusion that the cord blood test results reported in the Columbia study are not reliable means that the conclusions

reached in that study based on those test results are also not reliable. ***In other words, since the Columbia researchers' published conclusions are directly dependent on the cord blood testing that the SAP has found invalid and unreliable, EPA should not be relying on the Columbia study for any purpose*** related to regulatory decision-making. The 2016 RHHRA also lacks any definition of the specific neurodevelopmental effects allegedly caused by the theoretical exposures assumed by EPA and to be used as the new benchmark health effect. EPA speculates that these neurodevelopmental effects claimed to be associated with chlorpyrifos are caused by some mode of action other than cholinesterase inhibition. But EPA admits no such mode of action has been identified or validated. In addition, while EPA is claiming that animal studies increasingly show effects below the current PoD, EPA does not provide credible citations for such evidence in the RHHRA to allow independent peer review and comment. No SAP has ever considered let alone endorsed EPA's new precedent-setting approach.

EPA's proposed regulatory action also still relies on an overly conservative, screening-level drinking water assessment that is not adequately refined and far over-estimates levels found in the real world. Moreover, EPA's drinking water assessment ignores important, science-based refinements that DAS provided in a study submitted to the Agency in February 2016 and in comments submitted to previous dockets by DAS and other experts.

C. EPA's Regulatory Action for Chlorpyrifos Has Compromised Principles of Sound Science and Undermined Public and Stakeholder Confidence in the Regulatory Process.

Until now, EPA has developed its human health risk assessments for crop protection tools like chlorpyrifos by using the National Research Council's four-step process recommended for all regulatory agencies in 1983: (1) hazard identification, which examines whether a substance has the potential to cause harm to humans and if so, under what circumstances; (2) dose-response assessment, which analyzes the relationship between exposure and effects; (3) exposure assessment, which evaluates the frequency, timing and levels of contact with a substance; and (4) risk characterization, which explores how well the data support conclusions about the nature and extent of the risk assessment from exposure. Pursuant to EPA policies and statutory directives, this process is to be carried out in a transparent manner and based on valid, reliable, and replicable science.

But in the case of chlorpyrifos, EPA has not sufficiently or transparently addressed any of these elements and certainly has not done so on the basis of valid, reliable, and replicable data. The Agency has departed radically from its long-standing use of animal data to rely on a single epidemiological study for use in its risk assessment, notwithstanding the Agency's lack of access to the raw data supporting the study's conclusions. In doing so, EPA has cast aside dozens of toxicology studies generated over the last forty-five years, and disregarded other epidemiology studies—many done since the Columbia study—that do not support the Columbia researchers' conclusions. EPA has also been inconsistent in its recent regulatory actions with respect to chlorpyrifos, frequently shifting its conclusions and rationale. EPA's arbitrary and capricious approach is devoid of an adequate scientific basis, contravenes EPA's own process, statutory directives, and guidance, and has no place in 21st century risk assessment or regulatory decision-making.

EPA's actions also violate Due Process. Pesticide registrants are expected to retain all raw data and make them available to EPA for any study they submit. Not holding Columbia researchers to the same standard creates a glaring inconsistency and deprives DAS and other stakeholders assurance that the underlying raw data have been appropriately reviewed and the study's conclusions appropriately validated. EPA has also violated Due Process by failing to address voluminous comments already submitted by DAS, the U.S. Department of Agriculture ("USDA"), and other stakeholders in response to EPA's prior assessments and Proposed Rule. Indeed, DAS has submitted five separate sets of comments (four in 2016 alone) to which EPA has yet to respond.

The circumstances surrounding EPA's decision-making with respect to chlorpyrifos lead DAS to the unfortunate but inescapable conclusion that EPA changed its view on this critical agricultural tool not because of any new science relating to the product, but because of an abrupt and unprecedented change in regulatory policy during the late spring of 2015. That change in policy has driven the Agency's interpretation of science, instead of, more properly, good science leading to sound public policy. What has emerged is a series of inappropriate efforts by EPA to interpret the Columbia study in unprecedented, unsupportable, and invalidated ways that are not consistent with sound scientific methodology. EPA's 2016 RHHRA and drinking water analysis represent its latest efforts to inappropriately force science into a predetermined policy outcome. After decades of allowing growers to control pests on critical crops efficiently and safely, the

Agency has set a goal—the elimination of chlorpyrifos—and then manipulated a study never designed to drive the science on this issue in an effort to achieve that goal. This is inconsistent with good science and appropriate regulatory decision-making, and contrary to law.

Additionally, it appears that the Ninth Circuit's deadline for EPA to act on the Petition has given the Agency a convenient excuse to abandon Registration Review and favor expediency over established, scientifically sound analysis mandated by statute in order to implement its policy shift on chlorpyrifos. In its Proposed Rule and during the 2016 SAP proceedings, EPA repeatedly stated that it needs to act quickly in light of the court's approaching deadline. All evidence suggests that the Agency has been driven by this deadline, not by science-based decision-making pursuant to Registration Review.

The court's deadline, however, is not a reason for the Agency to rely on a study that is invalid for regulatory decision-making, and to conduct a less than robust drinking water assessment that ignores critical input. Simply stated, neither EPA's policy shift nor the court's deadline sanction arbitrary and capricious decision-making, the violation of the Due Process rights of DAS and other adversely affected parties, and the elimination of a critical tool for growers that has been supported for decades by robust toxicology data. But that is exactly what is occurring.

Instead of compromising its scientific standards and principles of sound government in order to appease the petitioners, EPA should have denied the Petition a long time ago and proceeded in conducting its risk assessment for chlorpyrifos in accordance with its scientifically sound historical practice.

Respectfully, EPA should deny the Petition and complete FIFRA's Registration Review process for chlorpyrifos, including the human health risk assessment, based on reliable, valid, and replicable data developed under established scientific standards, including the availability of the raw data. At the very least, EPA must delay a final action on chlorpyrifos until it has obtained independent SAP reviews of its unprecedented 2016 RHHRA and drinking water assessment.

II. Executive Summary

Expanding on the foregoing Introduction, for over forty-five years, EPA has set a PoD for chlorpyrifos based on cholinesterase inhibition and currently uses Red Blood Cell cholinesterase ("RBC ChEI").[5] This conservative and health-protective endpoint remains the gold standard used by regulatory bodies around the world, including EFSA and the World Health Organization. Numerous SAPs convened by EPA over the past eight years have confirmed their confidence in RBC ChEI as the appropriate regulatory standard. *See infra,* Section III.

In a radical shift in 2016, EPA instead proposed to set a PoD based on cord blood levels of chlorpyrifos reported in the Columbia study. The Agency convened an SAP meeting in April 2016 to review and comment on its unprecedented proposal. But the 2016 SAP rejected EPA's approach, concluding that cord blood measurements at birth were an insufficient basis to establish a PoD: "the majority of the Panel considers the Agency's use of the results from a single longitudinal study to make a decision with immense ramifications based on the use of cord blood measures of chlorpyrifos as a PoD for risk assessment as premature and possibly inappropriate." EPA, Transmittal of Meeting Minutes of the April 19–21, 2016 FIFRA SAP Meeting Held to Consider and Review Scientific Issues Associated with "Chlorpyrifos Analysis of Biomonitoring Data" ("2016 SAP Minutes"), at 18–19 (July 20, 2016). The SAP also expressed concerns with the lack of access to the underlying raw data supporting the study's conclusions, the lack of validation and replication of study results, the absence of practices to ensure the credibility of the research, and questionable approaches in analyses of the data. The Panel also questioned the underlying biological plausibility of a causal link between chlorpyrifos and the health effects, noting the Panel is not aware of any scientific evidence where such extremely small levels of chlorpyrifos in the blood reported in the Columbia study would lead to deleterious neurotoxicological effects in a mammalian system. *Id.* at 23. Many of these concerns with the Columbia study and the Agency's reliance on the study for unprecedented regulatory action have

[5] Acetylcholinesterase ("AChE") inhibition ("ChEI") is the mode/mechanism of action for effects to the mammalian system. EPA regulates on a particular type of AChE which is Red Blood Cell Acetylcholinesterase ("RBC AChE") inhibition, or simply Red Blood Cell cholinesterase ("RBC ChE") inhibition. RBC ChE inhibition is not an adverse effect in itself, but a marker of exposure and a conservative and protective endpoint that occurs well below levels required to inhibit other types of AChE that could be considered an adverse health effect.

been echoed by prior SAPs and other scientific experts and federal agencies. *See infra,* Section IV, and Appendix B, Deficiencies in the Columbia Study for Purposes of Risk Assessment.

Now, EPA's 2016 RHHRA advances yet another, completely new regulatory standard that is also based principally on the Columbia study. EPA's claimed justification for its new proposal is unsupported, not validated, and significantly overstates the SAP's conclusions. In particular, as support for its decision to propose a new regulatory standard for chlorpyrifos because of concerns over neurodevelopmental effects that allegedly occur at exposures below the current regulatory endpoint of 10% RBC ChEI inhibition, EPA claims that animal studies show effects below this threshold. But EPA has provided no credible support for this assertion and indeed, DAS has submitted to the Agency GLP-compliant animal data demonstrating *no effects* below the 10% RBC ChEI inhibition standard. Moreover, EPA's position that epidemiology studies, including the Columbia study, "suggest there is evidence" for adverse health outcomes purportedly associated with chlorpyrifos at exposures below levels that result in 10% RBC ChEI inhibition does *not* demonstrate causation at those levels and should not form the basis for precedent-setting regulatory action. *See infra,* Section V.

To be clear, nothing about the science being used as the primary underpinning of EPA's new approach—the Columbia study—has changed since EPA's last proposal that was rejected by the SAP. Instead, the Agency is proposing a new hypothesis that makes unsupported assumptions about how the subjects of the Columbia study *may* have been exposed to extremely small amounts of chlorpyrifos in their homes, but yet enough to result in the neurodevelopmental effects alleged in the study. The exposure assumptions the Agency now uses, however, are not validated and the claim of a causal linkage to neurodevelopment effects at exposure levels below the current regulatory standard is still unsupported by the science. *See infra*, Section VI.

Moreover, as set forth herein, there are a number of additional fundamental issues with EPA's new regulatory standard that raise significant scientific, policy, and legal concerns. First and foremost, EPA's approach is improperly founded on its unsupported assumption that there is a *causal* link between chlorpyrifos exposure below the current regulatory level and the neurodevelopmental effects reported in the Columbia study. With this assumption in place, EPA attempts to "calculate" the level of exposure that allegedly caused these effects, using assumptions about "crack and crevice" chlorpyrifos use nearly twenty years ago. However, in

doing so, EPA ignores the opportunity to compare this calculated level of exposure with data from multiple studies in which biomonitoring followed crack and crevice applications and which would be the accepted scientific practice for validation. Since the Agency's entire analysis rests on the Columbia study's published findings (which are in turn based on cord blood data the SAP deemed unreliable), the Agency's conclusions cannot stand. *See infra,* Section VI.A. The Agency's analysis also rests on unsupported and hearsay assumptions about chlorpyrifos use that grossly misrepresent exposure. *See infra*, Section VI.B.

In addition, EPA's calculation of a single value as the time-weighted average ("TWA") blood concentration discards the Columbia researchers' division of the study subjects into two "higher" and "lower" exposure groups and conclusion that subjects exposed to higher amounts of chlorpyrifos were more likely to demonstrate neurodevelopmental effects. EPA's present analysis based on assuming all receiving a crack and crevice treatment were exposed to the level causing the claimed effects thus concedes that there is no quantitative difference between the "higher" and "lower" exposure groups, and therefore there is no dose-response relationship attributable to chlorpyrifos. Without a valid dose-response relationship, the Agency remains unable to derive a plausible PoD for risk assessment purposes. *See infra,* Section VI.C.

Even though EPA claims that its new approach responds to the SAP's recommendations, EPA has taken significant leaps from what the SAP actually advised and taken a number of the SAP's key conclusions and recommendations out of context and ignored others. For example, EPA states that its latest TWA approach, a "hybrid approach" according to the Agency, is based on a recipe that the 2016 SAP provided. But that is simply incorrect, as the transcript from the SAP proceedings (submitted by DAS to NODA docket EPA-HQ-OPP-2015-0653) shows. *See infra*, Section VI.D.

In 2016, EPA proposed to the SAP that 2% reduction in working memory was the neurodevelopment effect that would be used as the health effect endpoint to be used to set the PoD. The SAP seriously challenged the significance of that level of reduction in working memory. In the RHHRA, EPA no longer cites that as the endpoint, but now does not even define the specific neurological effect being used. Defining a specific adverse outcome for specific dose level is the hallmark of regulatory risk assessment. *See infra,* Section VI.E.4.

In addition, EPA touts that its methodology is consistent with a "weight-of-the-evidence" approach, but then ignores over forty years of robust animal toxicology data, fails to acknowledge inconsistencies and even conflicting results across epidemiology studies, and improperly downplays epidemiology studies that reach a contrary conclusion. EPA has also failed to establish basic criteria to evaluate the credibility of the epidemiology it relies upon to develop a new regulatory standard—a fundamental failure noted by at least two SAPs. *See infra*, Sections VI.E.

EPA also must seek peer review on its new, precedent-setting regulatory standard, pursuant to statutory directives and Agency guidance. Taking final action in the absence of independent peer review raises further, significant Due Process concerns and would constitute arbitrary and capricious action. *See infra,* Section VI.F.

Further, EPA's continued use of the study without the underlying raw data, which the Columbia researchers have steadfastly refused to provide, is arbitrary and capricious under well-settled case law, does not meet fundamental standards of Due Process, and contravenes EPA's statutory obligations and Executive Branch directives. *See* Appendix C, Requests for Raw Data and Expressions of Concern About Absence of Raw Data. DAS and other stakeholders have submitted numerous prior comments to EPA on these issues, which the Agency has failed altogether to address. *See infra,* Section VII.; *see also* Appendix A. EPA's new PoD is unrealistically low and results in risk estimates that have no basis in fact. This is not surprising, however, given that the PoD determination was based on a fundamentally flawed TWA approach, unsupported assumptions about crack and crevice applications, and other serious deficiencies. *See infra,* Section X.

EPA has compounded its erroneous PoD with unfounded safety and uncertainty factors. In 2011, EPA recommended that its FQPA safety factor for chlorpyrifos be 1X due to the robust toxicology dataset in support of the registration. However, the Agency's 2016 RHHRA sets a 10X FQPA safety factor—resulting in an even lower permitted exposure level—and does so because the proposed new regulatory standard resulting from the crack and crevice scenario is considered a LOAEL (lowest observed adverse effect level) rather than a NOAEL (no observed adverse effect level). But this use of a LOAEL/NOAEL approach is totally inappropriate. Among other flaws, this approach ignores the statutory requirement that FQPA safety factors,

especially those used to revoke tolerances, must be based on valid, reliable data. *See infra*, Section VII.

In addition, EPA's decision to set a 10X intraspecies uncertainty factor is based on EPA's conclusion that the physiologically based pharmacokinetic ("PBPK") model for chlorpyrifos does not adequately address the life-stage of pregnancy. DAS has recently updated the PBPK model to account for this life-stage, and this work has been reviewed by independent scientific experts, who concluded that the changes to the model were sufficiently robust and validated to allow use by EPA and other regulatory bodies for risk assessments involving pregnant women. Accordingly, EPA should now be able to reduce the intraspecies uncertainty factor for pregnant women or women of childbearing age to 4X. *See infra*, Section IX.

Additionally, EPA's application of the FQPA Safety Factor to occupational risk assessment is inappropriate and leads to an inflated level of concern and overestimate of risk. EPA's residential post-application and bystander risk assessments also lack plausibility/reasonableness and ignore critical studies previously relied upon by the Agency. *See infra,* Section X.B.

Moreover, as set forth in detail herein, DAS is very concerned that EPA's proposed regulatory action relies on an unrefined drinking water assessment that is still based on screening-level modeling, is not adequately refined, and far over-estimates levels found in the real world. EPA's drinking water assessment ignores important, science-based refinements provided by DAS in a study submitted in February 2016 and in comments submitted to previous dockets by DAS and other experts. *See infra*, Section XI.

Finally, EPA's assessments ignore the significant economic impact of revocation of chlorpyrifos tolerances. U.S growers and farmers and the USDA have made clear the critical need for and value of this important crop protection tool in previous comments, which EPA has not acknowledged. U.S. growers, many of them small family farms, along with food processors and other distribution companies, will be severely impacted by EPA's proposed action. Global trade of key crops and crop products important to U.S. consumers will also be negatively affected. When combined, the economic impact could easily make the proposed revocation of tolerances a significant regulatory action. *See infra*, Section XII.

In sum, EPA is proposing regulatory action that is far from the "stepwise, objective, and transparent" process the Agency claims. In order to be consistent with established, good scientific methodology and rational regulatory decision-making, EPA should implement two steps immediately. First, EPA should convene an SAP(s) to review the Agency's 2016 RHHRA and drinking water assessment for chlorpyrifos. A formal request for SAP review has been submitted to the Agency by thirty-five major agricultural organizations. *See* Ex. 1. EPA has thus far asked for SAP review at every critical juncture with respect to its possible reliance on the Columbia study and other epidemiology studies to inform its decision-making. The 2016 RHHRA presents no less of an unprecedented approach to regulation, for the reasons set forth herein, and similarly demands SAP review. The court's deadline does not justify a failure to conduct thorough, science-based SAP review of EPA's unprecedented methodologies that are reflected in both the 2016 RHHRA and drinking water assessment.[6] Second, EPA should deny the Petition and postpone taking final action on chlorpyrifos until the Agency has completed Registration Review pursuant to FIFRA.

III. Regulatory History and Robust Toxicology Data Affirm that the Current Regulatory Standard for Chlorpyrifos Protects Human Health.

EPA sets exposure limits and bases its human health risk assessments for chemicals based on conservative and health-protective endpoints (also known as a point of departure or "PoD") that have historically been identified through required animal testing. For chlorpyrifos, inhibition of red blood cell ("RBC") cholinesterase ("ChEI") has always been (since chlorpyrifos was first registered more than forty-five years ago) the point of departure used by EPA and also

[6] In its December 21, 2016 Revised Human Health Risk Assessment for tetrachlorvinphos ("TCVP RHHRA"), EPA announced that it would be opening a comment period on a petition submitted by CropLife America asking the agency to "halt regulatory decisions that are highly influenced/determined by results of epidemiological studies that do not meet well-defined data quality standards, and that are not integrated into the health risk assessment in a transparent, well-defined manner." EPA said it would open this comment period based on its determination that any final action for TCVP "could potentially be impacted by EPA consideration of the epidemiological studies identified in the [CropLife] petition." TCVP RHHRA at 13. Because EPA's proposed revocation for chlorpyrifos is similarly based on epidemiological studies that do not meet well-defined data quality standards and that have not been integrated into EPA's risk assessment in a transparent manner, no decision should be made on chlorpyrifos until this review by EPA is complete.

remains the gold standard and point of departure used by the World Health Organization[7] and virtually all major global regulatory authorities. Numerous SAPs convened specifically by EPA over the last eight years have confirmed ChEI as the appropriate PoD for chlorpyrifos.

In a radical departure in 2016, however, EPA proposed to set the PoD for chlorpyrifos on cord blood levels in humans (the Columbia study) that are claimed to be associated with a non-specific and as yet unidentified and unvalidated effect and for which EPA has never received or reviewed the actual raw data. The most recent (2016) SAP rejected EPA's attempt to abandon the use of RBC ChEI in favor of using cord blood as the PoD from the Columbia study cohort. EPA's departure in approach after forty-five years is seemingly based on an abrupt change in regulatory policy, as there is no new science that would merit moving away from a conservative and health-protective endpoint that is used globally by all other regulatory authorities.

A. There is a Long and Well-Supported Regulatory History of Using Cholinesterase Inhibition as the Biological Endpoint Upon Which Risk Assessment for Chlorpyrifos is Based.

As noted earlier, acetylcholinesterase ("AChE") inhibition ("AChEI") is the mode/mechanism of action for effects of chlorpyrifos to the mammalian system. EPA regulates on a particular type of AChE which is Red Blood Cell Acetylcholinesterase ("RBC AChE") inhibition, or simply Red Blood Cell cholinesterase inhibition ("RBC ChEI").

To provide a succinct history of the Agency's consistent use of RBC ChEI as the point of departure, the following is provided beginning in 2000, although cholinesterase inhibition has always been used by EPA in its risk assessments for chlorpyrifos. In 2000, during its reregistration review for chlorpyrifos, EPA stated that "[i]nhibition of ChE is the most sensitive effect in all animal species evaluated and in humans, regardless of route or duration of exposure." EPA, Human Health Risk Assessment – Chlorpyrifos, at 2 (June 8, 2000). For risk assessment during the 2000 reregistration review, EPA used a combination of plasma, RBC, and brain ChEI from a variety of laboratory animal studies.

[7] The World Health Organization ("WHO") has completed multiple evaluations of chlorpyrifos toxicology and human safety since 1972. The WHO has consistently recognized acetylcholinesterase inhibition as the most sensitive toxicological effect of chlorpyrifos in mammals and established recommended risk assessment endpoints for human health protection based on acetylcholinesterase inhibition.

In 2008, EPA reaffirmed the use of ChEI as the appropriate PoD for chlorpyrifos specifically, stating that "[c]hlorpyrifos, like other organophosphates, binds to and phosphorylates the enzyme acetylcholinesterase (AChE) in both the central (brain) and peripheral nervous systems (USEPA, 1999), leading to accumulation of acetylcholine and, ultimately, to clinical signs of toxicity. This mode of action, in which AChE inhibition leads to neurotoxicity, has been well described (Mileson et al. 1999)." EPA, App. B – Mode of Action: Inhibition of Acetylcholinesterase (AChE), at 3 (Aug. 27, 2008). To put this reaffirmation in perspective from a timing aspect, Columbia study researchers started publishing in 2002 on exposure, and the infant outcome studies were first published in 2004. EPA was therefore aware of the Columbia study results when they reaffirmed ChEI as the appropriate PoD.

In its Science Issue Paper: Chlorpyrifos Hazard and Dose Response Characterization (USEPA, 2008), EPA stated that "[b]lood ChE inhibition was used as the endpoint for all scenarios." EPA, Science Issue Paper: Chlorpyrifos Hazard and Dose Response Characterization, at 9 (Aug. 21, 2008). This decision was confirmed by a FIFRA Scientific Advisory Panel (2008), which reviewed EPA's Issue Paper and stated that "cholinesterase inhibition should continue to be used for PoD until, at such time, an alternative mode of action is identified and validated." EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting held September 16–18, 2008 on the Agency's Evaluation of the Toxicity Profile of Chlorpyrifos, at 12 (Dec.17, 2008) ("2008 SAP Minutes"). No such alternative mode of action has been identified or confirmed to the present day. It is also important that this SAP concluded that "[t]he Panel agreed that the epidemiological studies have utility for risk assessment, but not as the principal basis for characterization of the point of departure (PoD)." *Id.* at 10.

In 2009, EPA issued its Revised Human Health Assessment Scoping Document in Support of Registration Review and again noted that "[i]nhibition of ChE was the most sensitive effect in all animal species evaluated." EPA, Chlorpyrifos. Revised Human Health Assessment Scoping Document in Support of Registration Review, EPA-HQ-OPP-2008-0850-0003, at 2 (Feb. 9, 2009). In the Scoping Document, EPA stated that "[t]he scoping team concluded that the only new toxicology data needed at this time to support the registration review of chlorpyrifos is an immunotoxicity study and an acute and repeated comparative cholinesterase assay (CCA) study." *Id.* There was no indication at this time, nor any new data to suggest that

investigations in animals were needed to explore possible other modes of action or to determine if effects were occurring below 10% RBC ChEI.

In 2011, in its Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration Review, EPA affirmed that "[t]he toxicology database for chlorpyrifos is substantially complete (40 CFR 158.340 guideline studies have been submitted) and has been used to characterize toxicity and for selecting points of departure for purposes of the current risk assessment." EPA, Chlorpyrifos Preliminary Human Health Risk Assessment for Registration Review ("PHHRA"), at 7 (June 30, 2011). Further, the Agency said that it "is maintaining, at this time based on available data, that cholinesterase inhibition (ChEI) provides the most sensitive dose-response information for deriving points of departure for chlorpyrifos. In animals, significant inhibition of plasma and red blood cell (RBC) ChE occur at doses below those that cause brain ChE inhibition." *Id.*

EPA convened a Scientific Advisory Panel in 2012 to review the available animal toxicological data for chlorpyrifos. In its first question (Question 1), EPA again reaffirmed cholinesterase inhibition as the primary mode of action and stated "AChE data remain the most robust dose-response data for deriving points of departure" and asked the SAP to confirm:

> *EPA Question 1.0:*
>
> It is well established that AChE inhibition is the primary mode of action/adverse outcome pathway for OPs, like chlorpyrifos. Because AChE inhibition is the initiating event for this mode of action/adverse outcome pathway, using AChE inhibition as a regulatory endpoint is protective of downstream cholinergic effects. Moreover, historically, given the sensitivity of AChE inhibition data for OPs, these data have been considered to be protective of other potential toxicities and/or modes of action for OPs. In 2008, the Agency performed a comprehensive review of the available AChE data from multiple lifestages. This review has been supplemented with the newest studies. Consistent with the recommendations from the 2008 SAP, the Agency believes that AChE data remain the most robust dose-response data for deriving points of departure in *in vivo* experimental toxicology studies with laboratory animals. *Please comment on the Agency's preliminary conclusion that AChE data remain the most robust source of data for deriving points of departure for chlorpyrifos. Please include a discussion of the strengths and uncertainties of this preliminary conclusion.*

EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting held April 10–12, 2012 on "Chlorpyrifos Health Effects" ("2012 SAP Minutes") at 12 (July 11, 2012). The 2012 SAP Panel Response notes that all studies reporting neurobehavioral effects

following exposures have shown AChEI also occurred. Again, this SAP was convened after the Columbia study published articles were initially available:

> The Panel concurs with the Agency's position that AChE data continue to be the strongest resource of data for deriving points of departure for chlorpyrifos. The Panel's conclusion is based on the premise that all studies reporting neurobehavioral changes following *in vivo* prenatal or postnatal exposures to chlorpyrifos have been accompanied by AChE inhibition when measured at an appropriate time following administration of chlorpyrifos.

Id. The Panel also weighed in on studies that purport to demonstrate neurodevelopmental effects either below 10% RBC ChEI or through a non-cholinergic mode of action and concluded that:

> [S]tudies evaluating neurodevelopmental effects entailed experimental designs that do not permit an efficient means of determining a point of departure for chlorpyrifos. Thus, just as in the 2008 SAP, this Panel advises that the Agency continue to use AChE data at the most sensitive lifestages for dose-response analysis and deriving points of departure. Also in keeping with the 2008 SAP, this Panel expresses concern about the use of Dimethyl Sulfoxide (DMSO) as a vehicle because of its intrinsic toxicity, its potential influence on absorption and interaction with chlorpyrifos, and the impact of this interaction on the developing organism.

Id. In 2014, upon release of the Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review, EPA employed a PBPK model for chlorpyrifos in determining a PoD. *See* EPA, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (Dec. 29, 2014) ("2014 RHHRA"). EPA continued, however, to propose 10% inhibition of RBC ChEI as its regulatory standard. Use of the PBPK model also allowed the reduction of the interspecies (animal to human) extrapolation factor and intraspecies (across humans) extrapolation factor for the general population.

As recently as late 2015, in its Proposed Rule, EPA affirmed its confidence in its current regulatory standard, stating that "AChE inhibition remains the most robust quantitative dose response data for chlorpyrifos and thus continues to be the critical effect for the quantitative risk assessment." Proposed Rule, Fed. Reg. at 69,087. The Agency observed that this approach is consistent with advice of the 2008 and 2012 SAPs, which were specifically charged with evaluating the Agency's approach to evaluating the toxicity of chlorpyrifos. *Id.*

But then EPA made a radical shift in proposing to change the "PoDs from doses eliciting 10% RBC . . . AChE inhibition to adverse effects changes in neurodevelopment as measured by

epidemiology studies conducted by [the Columbia study]." 2016 SAP Minutes at 10. In effect, what EPA did was abandon its long-standing position (and multiple SAP recommendations) that cholinesterase inhibition represents the most sensitive and robust endpoint for risk assessment and move abruptly to what EPA described as "the conceptual approach to using the cord blood data to derive PoDs for women of childbearing age, . . . infants, and children." EPA, Chlorpyrifos Issue Paper: Evaluation of Biomonitoring Data from Epidemiology Studies, EPA-HQ-OPP-2016-0062-0005 at 11 (Mar. 11, 2016) ("Chlorpyrifos Issue Paper"). However, EPA's proposal was not based on new information, but rather a 2011 publication of the Columbia study, in which the study authors reported decrements in Working Memory, an index of the IQ test. The fact that this move in 2016 was based on information that was available some five years earlier and before the various reviews cited above suggests EPA's current proposal is based on a dramatic shift in regulatory policy rather than science. This move also signified that EPA was going to abandon its reliance on animal toxicology data, the standard that has been in place since chlorpyrifos was first registered in the United States.

Following release of its proposal, EPA convened yet another SAP (2016) on its proposed approach to using cord blood from the Columbia study as the PoD. The Panel stated that:

> The majority of the Panel did not agree with the Agency's use of the results from a single longitudinal study to make a decision based on the use of cord blood measures of chlorpyrifos as a PoD for risk assessment. . . . The majority of the Panel stated that using cord blood chlorpyrifos concentrations for derivation of the PoD could not be justified by any sound scientific evaluation.

2016 SAP Minutes at 18–19.

Despite the SAP's strong recommendation to *not* use the Columbia study data for derivation of a PoD, *see* 2016 RHHRA at 3 ("The 2016 SAP did not support using the cord blood quantitatively for deriving PoDs."), the Agency, in November of 2016, released the current RHHRA. In this revised assessment, the Agency has departed even more from standard and long-standing risk assessment approaches by assuming an exposure (gathered from phone conversations with former crack and crevice applicators; no actual data used) to pregnant women who gave birth to children from the Columbia study and for which there is a purported, yet undefined neurodevelopmental effect associated with those children.

B. EFSA Review of Epidemiology Studies Confirms that the Current Regulatory Standard is Appropriate.

A recent reevaluation of chlorpyrifos-related toxicology and selection of regulatory endpoints for human health was completed by the EFSA on behalf of the European Commission (EFSA, 2014). Chlorpyrifos had been included in Annex I (list of approved active substances) to Directive 91/414/EEC during 2006 as part of the EU Review process. In 2012, a data call-in for submission of new studies completed since the time of the EU Review was issued, and these new studies were first evaluated by Spain, the rapporteur member state, and subsequently subjected to peer review under the auspices of EFSA. The result of the EFSA peer review was that "[t]he experts agreed on the use of the Red Blood Cell cholinesterase inhibition to derive the reference values." EFSA J. 2014; 12(4):3640 at 2. This represented a change in approach in that, previously, endpoints for chlorpyrifos and other organophosphorus insecticides had been established based on brain cholinesterase inhibition and/or observation of cholinergic symptoms. Accordingly, EFSA took its recommendations for further peer review by its Panel on Plant Protection Products and their Residues ("PPR Panel") during 2014. The PPR Panel endorsed the proposed acetylcholinesterase-based Acceptable Daily Intake, Acute Reference Dose, and Acceptable Operator Exposure Level proposed by EFSA. This action thus aligned the endpoint with the RBC ChE inhibition endpoint previously used by EPA, but not the dramatically lower endpoint currently proposed by EPA in the 2016 RHHRA.

As part of the European Commission reevaluation of chlorpyrifos toxicology and human health (EFSA, 2014), EFSA paid particular attention to the results of studies, including those being cited by EPA (Lovasi et al. 2011; Rauh et al. 2012; Rauh et al. 2011; Rauh et al. 2006; Whyatt et al. 2009; Whyatt et al. 2007; Whyatt et al. 2004), the Mount Sinai Hospital Children's Environmental Health Cohort (Berkowitz et al. 2004; Engel et al. 2007; Engel et al. 2011) (the "Mt. Sinai study"); and the UC Berkeley's Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) Cohort (Bouchard et al. 2011; Eskenazi et al. 2004; Eskenazi et al. 2010; Eskenazi et al. 2007; Harley et al. 2011; Marks et al. 2010; Young et al. 2005) (the "CHAMACOS study"). The EFSA peer review made the following conclusion regarding these studies:

> The epidemiology data are not sufficiently robust to support the hypothesis that CPF is a causal factor for neurodevelopmental effects. Exposures in the epidemiology studies are at least 1000-fold lower than those used in the animal

> studies, but the animal toxicity data do not provide clear evidence that CPF is associated with neurodevelopmental effects at doses that are below the threshold for inhibition of AChE in the brain…. Although multiple mechanisms have been proposed to explain the neurodevelopmental effects of chlorpyrifos, a coherent mode of action with supportable key events, particularly with regard to dose-response and temporal concordance, has not been elucidated yet.

EFSA. (2014). Final addendum to the Art. 21 Review on chlorpyrifos – public version – Initial risk assessment provided by the Rapporteur Member State Spain for the existing substance CHLORPYRIFOS as referred to in Article 21 of regulation (EC) No. 1107/2009. February, 2014. Chapter: Add. III to Vol. 3, Ch. 6 to DAR. Pg. 53-54. University researchers (Ntzani et al. 2013), under contract with EFSA reviewed the epidemiology studies published since 2006. They concluded there is no evidence to suggest an association between pesticide exposure, including chlorpyrifos, and neurodevelopmental effects. As previously described, EFSA (2014) also supported the use of RBC ChE as the most appropriate endpoint for assessing health risks from chlorpyrifos, and concluded the epidemiology data are not sufficiently robust to support a causal relationship with neurodevelopment effects.

* * *

In sum, over the course of the Registration Review for chlorpyrifos since 2008, EPA has moved from a consistent, long-standing, and conservative approach (and one that is used globally by regulatory authorities) of using RBC ChEI based on a complete toxicological database to an approach that is based on speculative exposure data and an undefined effect in children based on one epidemiological study for which EPA has never received nor reviewed the raw data. DAS has previously commented on both RBC ChEI as the conservative PoD as well as the limitations of the Columbia study for use in risk assessment, but to date, EPA has not provided any response to those comments.

References:

EFSA. (2014). Final addendum to the Art. 21 Review on chlorpyrifos – public version – Initial risk assessment provided by the Rapporteur Member State Spain for the existing substance CHLORPYRIFOS as referred to in Article 21 of regulation (EC) No. 1107/2009. February, 2014. Chapter: Add. III to Vol. 3, Ch. 6 to DAR. Pg. 53-54.

Mileson, B.E., Chambers, J.E., Chen, W.L. et al. 1998. Common Mechanism of Toxicity: A Case Study of Organophosphorus Pesticides. Tox. 41:8-20.

Ntzani EE, Chondrogiorgi M, Ntritsos G, Evangelou E,Tzoulaki,I. (2013). Literature review on epidemiology studies linking exposure to pesticides and health effects. EFSA supporting publication 2013: EN-497. 159 pp.

EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting held April 10–12, 2012 on "Chlorpyrifos Health Effects" (July 11, 2012).

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EPA, Chlorpyrifos Issue Paper: Evaluation of Biomonitoring Data from Epidemiology Studies, EPA-HQ-OPP-2016-0062-0005 (Mar. 11, 2016).

EPA, Transmittal of Meeting Minutes of the April 19–21, 2016 FIFRA SAP Meeting Held to Consider and Review Scientific Issues Associated with "Chlorpyrifos Analysis of Biomonitoring Data" (July 20, 2016).

EPA, Chlorpyrifos Revised Human Health Risk Assessment for Registration Review (Nov. 3, 2016).

IV. The 2016 SAP, USDA, and Other Experts Have Consistently Challenged EPA's Unprecedented Attempt to Set a New Regulatory Standard for Chlorpyrifos on the Basis of the Columbia Study.

EPA sought guidance from the April 2016 SAP on its proposal to set a new regulatory standard on the basis of the Columbia study. The Panel raised numerous and significant concerns with EPA's use of the Columbia study to inform regulatory action, in particular the use of a single cord blood measurement to estimate exposure and the lack of biological plausibility for a causal link between chlorpyrifos and health effects at the extremely low levels reported in the Columbia study, among others. *See, e.g.,* 2016 SAP Minutes at 22–23. The Panel also expressed concerns with the lack of raw data; the lack of validation and replication of study

results; the absence of practices to ensure the credibility of the research; and questionable approaches in the analyses of the information reported in the published articles about the study. *Id.* at 41, SAP Tr. at 89. The SAP's concerns are consistent with those of other scientific and regulatory experts, USDA, and several prior SAPs.

A. The 2016 SAP Did Not Agree with EPA's Proposal to Rely on the Columbia Study, Given its Deficiencies and Limitations, and Concluded that Cord Blood Measurements at Birth Were an Insufficient Basis to Establish a Point of Departure.

The SAP strongly discouraged EPA from setting a new PoD for chlorpyrifos based on reported cord blood information from the Columbia study. The Panel considered "the Agency's use of the results from a single longitudinal study to make a decision with immense ramifications based on the use of cord blood measures of chlorpyrifos as a PoD for risk assessment [to be] premature and possibly inappropriate." 2016 SAP Minutes at 25. The SAP was unequivocal in its assessment that EPA's proposal was contrary to proper scientific methodology: "[t]he reliance on a single cord blood measurement from only one study, *i.e.*, the Columbia study, as the primary basis for a highly impactful regulatory decision, appears to go against standard practices of science in the field of toxicology and pharmacology." SAP Tr. at 537–38.

Moreover, many Panel members expressed their concern about the validity of the cord blood results. *See, e.g.,* SAP Tr. at 89 ("I disagree with the validity of the cord blood data, really."); *id.* at 501 ("But you know, I personally don't really think that cord blood is usable as an exposure assessment for anyone here, really."). Panel members further criticized the lack of replication of study results; the fact that Good Laboratory Practices ("GLPs") were not in place to ensure the credibility of the research; and, questionable approaches in the analyses of the data. 2016 SAP Minutes at 22–23. The Panel also questioned the underlying biological plausibility of a causal link between chlorpyrifos at levels reported in the Columbia study and the health effects reported, noting the Panel is not aware of any scientific evidence where pg/g levels in the blood would lead to deleterious neurotoxicological effects in a mammalian system. *Id.* at 23. And while EPA argued at the 2016 SAP that the validity of the Columbia study should be accepted, even without access to the raw data, since the research papers had been peer-reviewed by the publishing journals, the Panel concluded such review of research studies cannot be equated to studies designed under GLP or Clinical Laboratory Improvement Amendments ("CLIA")

standards, especially when measurements and conclusions have not been independently replicated. *Id.* at 41.

The 2016 SAP members also challenged EPA's proposal to use a 2% reduction in Working Memory as the benchmark health effect for setting a PoD. Panel members raised serious concerns regarding the lack of biological plausibility for how low cord blood (low parts per trillion) concentrations of chlorpyrifos can alter Working Memory and produce neurodevelopmental impairment, and concluded that the Agency provided insufficient justification to utilize this methodology. SAP Tr. at 536 ("Without any evidence in the animal literature or elsewhere of this mechanism of action, that could explain how pg/g levels in the blood could impair IQ and/or Working Memory there does not appear to be a biological plausibility.").

The numerous concerns raised by the SAP seriously undermine the Agency's reliance on cord blood to establish a point of departure. Most importantly for purposes of EPA's 2016 RHHRA, because the SAP has concluded that the cord blood test results reported in the Columbia study's published findings are invalid and unreliable (and without the raw data to properly assess the reliability and validity of the study's findings) any conclusions reached based on the study's findings are, by extension, inherently unreliable and cannot form the basis for regulatory action. This is particularly true as to a regulatory action with ramifications as significant and far-reaching as tolerance revocation.

B. The 2016 SAP, Other Experts, and Another Federal Agency Have Identified Numerous Additional Deficiencies in the Columbia Study for Purposes of Risk Assessment.

Beyond EPA's improper reliance on the Columbia study's published cord blood results, the SAP, USDA, and other experts have raised a host of very significant concerns about any effort by the Agency to rely on the Columbia study for purposes of regulatory decision-making. For example, the SAP's deep concern regarding the absence of the raw data for the Columbia study transcends the cord blood issue and goes to the heart of any reliance on the study for regulatory purposes:

> [I]t's been said several times, having data would help people draw their own conclusions, including the agency, on how to proceed. . . . *[N]ot having data was just amazing, flabbergasting. What's going on?* . . . In order for a registrant to put a new pesticide on the market or to re-register a pesticide the data has to be very

> vigorous. Now we're looking at something the opposite. . . . So if we're basing this on one study where it's not been reproduced, you can't get the actual hard data, there's lots and lots of points below levels of detection, one has to give that really serious thought.

Id. at 494, 766 (emphasis added).

The SAP also expressed significant concerns about other aspects of the Columbia study, including the lack of replication, reliance on one study for such a critical regulatory decision, and the absence of generalizability:

- "Now I know you're on a deadline, but again, given the national and possibl[e] international ramifications of such a point of departure one would at least like to see replication." SAP Tr. at 627;

- "I don't believe epidemiology alone should drive the decision of such magnitude like this. . . . [T]here's not enough evidence to change the current [point of departure] guidelines." *Id*. at 769;

- "I'm concerned about . . . using one epi study for risk assessment. That really gives me a lot of pause. . . . [U]sing one study does set sort of a bad precedent." *Id.* at 771–72.

- "I disagree with the validity of the cord blood data, really." *Id.* at 89;

- "[The Columbia Study] is plagued by issues that diminish the enthusiasm for this study and create a host of uncertainties." *Id.* at 622;

- "I would feel uncomfortable trying to make regulations or policy [based on the Columbia Study] because I don't think the data are very strong." *Id.* at 768.

In connection with the 2016 SAP, other scientific and regulatory experts also noted numerous deficiencies with the Columbia study. For example:

> [t]he published articles [for the Columbia study] fail to account for iron deficiency and the paternal IQ, and the medical records assessment (*e.g.*, Apgar scores, maternal medication) and analysis are not explained. In addition, the articles fail to account for socioeconomic stressors, including alcohol and drug use and violence, which have been proven to have a direct impact on neurodevelopmental outcomes. Consequential exposure to other toxins such as lead and other non-organophosphate chemicals may also be important, but are not adequately addressed. Perhaps most concerning, however, is the published articles' failure to accurately account for gestational age . . . as a confounding variable. New lines of research have demonstrated that gestational age has a significant effect on neurodevelopmental outcomes. The difference of even one week in a baby's age at birth can lead to adverse neurodevelopmental effects, including lower scores on

> the Bayley scales of mental and motor development. This research has led to changes in obstetrical practices during the time of the Columbia Study.

Dr. Banner Comments at 5–6, EPA-HQ-OPP-2016-0119 (Apr. 18, 2016) ("Dr. Banner Comments") (citations omitted).[8] In addition, these experts echoed the SAP's concerns regarding use of the study for regulatory purposes in the absence of the raw data. *See, e.g.,* Decl. of Dr. Rita Schoeny In Supp. of Br. of *Amici Curiae* CropLife America ¶ 21, *PANNA v. EPA*, No. 14-72794 (9th Cir. July 5, 2016), ECF No. 40-12 ("Regardless of the regulatory standard EPA ultimately adopts, the absence of the raw data underlying the Columbia Study and a thorough analysis of that raw data present key scientific vulnerabilities to the Agency's assessment for chlorpyrifos."), Ex. 2; Dr. Banner Comments at 4, Ex. 3 ("It is troubling and inexplicable to me that the Columbia Study investigators have not made the raw data underlying this taxpayer-funded research publicly available, and even more so that EPA is emphasizing the importance of the Study in guiding its regulatory action in the absence of the raw data. Details of the Study methods and raw data allow for the replication and understanding of scientific studies. Providing the data for scientific evaluation and peer-review is an integral part of the scientific process and is a standard practice in many disciplines. It is especially crucial with complex databases where multiple methods of analysis may be employed and the final results may not completely reflect all of the methods in use."). EPA has not even acknowledged, let alone addressed, these deficiencies in its 2016 RHHRA.

Following the 2016 SAP report, DAS convened a panel consisting of former senior government officials and independent expert consultants with extensive scientific and regulatory experience to address several charge questions related to EPA's regulatory action with respect to chlorpyrifos (the "Expert Panel" or "Panel"). Specifically, the Panel was asked to provide its scientific opinion regarding EPA's proposed use of the Columbia study in the current chlorpyrifos human health risk assessment. The Panel included members with expertise in epidemiology, FQPA statutory language and interpretation, exposure assessment, reproductive and developmental toxicology, regulatory risk assessment, and dose response assessment. The

[8] Dr. Banner's Comments, which are attached as Exhibit 3 and incorporated herein, raised numerous additional limitations and deficiencies in the Columbia Study.

Panel identified numerous concerns with the Columbia study and expressed its strong disapproval of the use of the study for regulatory decision-making:

> The Expert Panel notes that specific issues that limit the quality, validity, completeness, and reliability of the [Columbia] data were described in this Report, by OPP's Scientific Advisory Panel, by other scientists in a previous report submitted to the Agency (Goodman et al. 2016) and/or by other agencies. The extent and degree of concordance in assessment of these issues is striking. Further, the issues raised are not minor, but, in fact, are fundamental to the development of robust and credible data that can withstand scrutiny. Issues that have been found to be highly problematic for the [Columbia] studies include:
>
> - The studies lack longitudinally-designed analyses with repeated exposure and outcome (and if needed, confounder) measures.
> - The studies do not include exposure assessments taking into account relevant timing (e.g., multiple sampling points) as well as consideration of method sensitivity, biomarker specificity and stability, matrix adjustment considerations, and sample contamination.
> - The study analyses may have inadequately controlled for important confounders.
> - The studies do not include sensitivity analyses including formal assessment of bias that address the inherent uncertainty of observational research.
> - There is evidence that the reported associations lack within-study consistency and are in disagreement with findings from other studies.
>
> **Recommendation:** The Expert Panel recommends that *OPP not rely on the [Columbia] cohort study as the basis for its chlorpyrifos risk assessment as the data do not meet the criteria of quality, validity, completeness, and reliability*.

Food Quality Protection Act (FQPA) Expert Panel Report, at 11 (Oct. 17, 2016), Ex. 4 (emphasis added).

USDA has also called into question EPA's reliance on the Columbia study in regulatory decision-making, asserting that EPA's decision to base "application of an additional FQPA safety factor on epidemiological evidence appears to be a novel application." USDA Public Comments on the Chlorpyrifos, Tolerance Revocations, a Proposed Rule published in the Federal Register on Nov. 6, 2015; EPA docket EPA-HQ-OPP-2015-0653 at 4, EPA-HQ-OPP-2015-0653-0369 (Jan. 5, 2016). USDA also requested "that the data underlying the foundational epidemiologic studies supporting EPA's human health risk assessment for chlorpyrifos be procured by EPA and released for expert peer review." *Id.* at 5. Finally, USDA noted numerous deficiencies in the methodology of the epidemiological studies relied on by EPA (including the

Columbia study), such as whether the study adequately considered other confounding factors and employed appropriate statistical techniques. *Id.* at 6.

C. The 2016 SAP's Conclusions About the Columbia Study Are Consistent with Three Prior SAPs.

EPA has convened several SAPs to provide guidance on issues relating to the epidemiologic research studying chlorpyrifos. All three SAPs identified shortcomings and other concerns with the Columbia study that EPA has failed to adequately address or even consider. *See also* DAS Response to EPA's 2014 RHHRA at 11, Dow AgroSciences LLC's Response to EPA Revised Human Health Risk Assessment for Chlorpyrifos Registration Review, EPA-HQ-OPP-2008-0850-0845 at 35.

1. Limitations Raised by the 2008 SAP and in EPA's 2011 PHHRA

In September 2008, EPA convened an SAP to provide a preliminary review of experimental toxicology and epidemiology data available at that time, including the Columbia, Mt. Sinai, and CHAMACOS studies. The SAP found that "it cannot be stated that chlorpyrifos is the sole contributor to the observed outcomes" and due to the limitations in the studies, discouraged EPA from using the studies quantitatively in risk assessment. EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held September 16–18 on the Agency's Evaluation of the Toxicity Profile of Chlorpyrifos (the "2008 SAP Minutes") at 13, 37.

In its 2011 PHHRA, EPA considered these three federally funded epidemiology studies, as well as the 2008 SAP review of them, and identified numerous limitations with the studies. PHHRA at 29–34. In particular, EPA discussed the SAP's findings that the Columbia study subjects were exposed to multiple chemicals and other OPs. PHHRA at 32. EPA also observed that the Columbia study subjects "are from low income multi-ethnic populations and urban neighborhoods and may experience other exposures that may also influence neurodevelopmental outcomes." PHHRA at 33. EPA acknowledged the 2008 SAP's recommendation that epidemiology studies not be considered quantitatively for deriving PoDs. PHHRA at 33. EPA concluded in its PHHRA that it would "carefully consider the strengths and limitations of the epidemiology studies *along with the available empirical data* in a full weight of evidence analysis in the final [human health risk] assessment." PHHRA at 34 (emphasis added).

2. Limitations Raised in 2012 SAP

In April 2012, EPA convened another SAP to review the Agency's preliminary conclusions regarding a "weight-of-evidence" approach to integrating epidemiologic research with the experimental toxicology studies for the neurodevelopmental outcomes and AChE inhibition. The 2012 SAP also identified several weaknesses and other concerns with respect to the epidemiologic research, including the Columbia study. In particular, the panel found that it was "very difficult" to attribute the effects observed to a single chemical, given that the subjects were exposed to multiple chemicals over a multi-year period and given the complexities in a child's brain maturation process. 2012 SAP Minutes at 17, 45 ("[I]t cannot be stated that chlorpyrifos is the sole contributor to the observed outcomes."); *Id.* at 42 (cautioning against "identifying any one specific chemical as the main one associated with the cognitive deficits observed at 7 years of age in the Columbia cohort.") The panel also raised concern about "the modest sample sizes of the studies," which it deemed "one of the most important limitations of these studies [including the Columbia study]." 2012 SAP Minutes at 17–18.

The 2012 SAP further observed that the epidemiology studies, including the Columbia study, were insufficient to derive a PoD. The panel recognized "the limitations of estimating chlorpyrifos exposures based on the exposure measures collected in [the Columbia study, the Mt. Sinai study, and the CHAMACOS study]" and thus "concur[red] with EPA that the data generated from these studies alone [were] *not adequate enough to obtain a point of departure (POD) for the purposes of quantitative risk assessment*." *Id.* at 19 (emphasis added); *see also id.* at 50 ("[T]he use by the three studies of different exposure matrices . . . and different targeted analytes . . . [made] the effort of deriving a definitive POD based on those data alone impossible."). Importantly, the panel found that the three epidemiology studies under consideration, including the Columbia study, "were primarily focused on assessing health outcomes associated with a variety of environmental factors, and *were not designed to conduct a quantitative exposure assessment for chlorpyrifos*." *Id.* (emphasis added).

3. Limitations Raised in 2012 Federal Peer Review

In 2012 EPA sought input from scientists within the federal government regarding a 2012 published article describing the results of magnetic resonance imaging on a subset of the children in the Columbia study (the "2012 Federal Peer Review"). The 2012 Federal Peer Review also

discussed several limitations and other concerns with the Columbia study, including the small sample size and use of a general IQ measure to quantify cognition:

> The results [of Rauh et al. (2012)] must be interpreted very cautiously since there were only 6 males in the high exposure group and 9 in the low exposure group . . . . The study only used a general IQ measure to quantify cognition in this study and more specific cognitive and behavioral tests would be needed to pinpoint specific cognitive processes affected by CPF exposure.

Comments from Dr. Freund to EPA Aug. 3, 2013 Request for Peer Review at 1–2. The Federal Peer Review also questioned the generalizability of the findings, highlighting the "need for future research with larger samples and other populations." Comments from Dr. Bitsko to EPA Aug. 15, 2012 Request for Peer Review at 1; *see also* Comments from Dr. Chelonis at 2 (observing that "given that the sample of children used in the Rauh et al. studies had very different characteristics than that of the samples on which these [psychological] measures were standardized, observing that caution should be used when describing the results, *especially when attempting to generalize these findings to the general population*") (emphasis added). Finally, the Federal Peer Review considered the possibility that lead could have impacted the study's findings, because "there is evidence that even low levels of lead can impact neurodevelopment, and even that the observed neurobehavioral deficits are more pronounced at lower blood lead levels when compared with higher blood lead levels." Comments from Dr. Bitsko to EPA, July 23, 2012 Request for Peer Review at 1–2 (citations omitted) (emphasis added). While it had been "reported that lead was not associated with chlorpyrifos; however, given the sample size, *this may not be a reliable finding*." *Id.* (emphasis added).

* * *

Clear from the foregoing comments from multiple SAPs and other experts is that the Columbia study is simply not sufficiently robust to be used in regulatory decision-making. *See, e.g.*, Declaration of Jennifer Seed in Supp. of Br. of *Amici Curiae* CropLife America, ¶ 24, *PANNA v. EPA*, No. 14-72794 (9th Cir. July 5, 2016), ECF No. 40-11, Ex. 5 ("Because of the numerous limitations with the Columbia study that have been identified by several SAPs and other sources, it is not clear to me that there will ever be a rational, science-based justification for EPA to use the Columbia study as a basis for a new regulatory standard for chlorpyrifos or otherwise rely on it for its regulatory decision-making for chlorpyrifos until such time that the

findings are confirmed in other populations, including adequate blood sampling at appropriate timepoints for chlorpyrifos.").

V. EPA is Relying on a Flawed Assumption Concerning any Demonstrated Link Between Noncholinergic Effects and Chlorpyrifos Exposures at Ultra Low Concentrations.

As justification for its precedent-setting approach for the risk assessment of chlorpyrifos because of concerns over neurodevelopmental effects that might occur below an exposure level associated with 10% RBC ChEI, EPA claims that animal studies increasingly show effects below this threshold. Neither EPA nor the SAP Minutes, however, provide credible citations pointing to such evidence. In addition, there is no new science that demonstrates effects from toxicological studies below a threshold of 10% RBC ChEI. Perhaps most importantly, there *does* exist GLP-compliant and EPA-required research conducted by the registrant on chlorpyrifos that demonstrates no effects below a threshold of 10% RBC ChEI, but EPA fails to recognize or cite this research. Moreover, the few studies that EPA references as supportive of effects below 10% RBC ChEI have significant experimental challenges that both EPA and the SAP have recognized but are currently ignoring. EPA has not provided, and SAPs have confirmed, that there is no known toxicological mode of action that would be associated with effects below a threshold of 10% RBC ChEI and as such, no animal model that would support the contention that epidemiological studies associate exposure to chlorpyrifos with neurodevelopmental outcomes below a threshold of 10% RBC ChEI. Finally, regarding human epidemiological evidence, the suggestion that there is evidence for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% RBC ChEI is not a demonstration of causation. The mere suggestion of an association should not form the basis for a precedent-setting regulatory action and warrants further rigorous study

A. EPA Fails to Provide Credible Evidence Demonstrating Adverse Health Outcomes in Animal Studies with Chlorpyrifos Exposures Below a Threshold Associated with 10% RBC ChEI.

1. The SAP Did Not Confirm or Fully Support that Toxicological Studies Support Effects Below 10% RBC ChEI.

In its current 2016 RHHRA, the Agency states that the 2016 SAP "concluded that epidemiology and toxicology studies suggest there is evidence for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% RBC AChE inhibition,

which was used as the POD in the EPA's 2014 RHHRA and for the 2015 proposed revocation rule." 2016 RHHRA at 3. DAS is concerned that while EPA is contending that the Columbia study purports to show an association between chlorpyrifos exposure below a level corresponding to less than 10% RBC ChEI and neurodevelopmental effects, there is now the additional suggestion that toxicology studies also suggest effects below 10% RBC ChEI. There is, however, no credible scientific evidence to support this contention. Neither the recent 2016 SAP nor EPA's 2016 RHHRA provide a single scientific citation to support this contention.

In addition, a more complete review of the SAP minutes demonstrates that the 2016 SAP made several qualifying statements that undermine EPA's position that the toxicological database supports its newly proposed action. In particular, the SAP minutes state as follows:

> There is an accumulating body of animal and in vitro evidence to suggest that organophosphates affect a variety of biological targets in addition to acetylcholinesterase (AChE). A few of these studies suggest that these targets may even be affected at levels that are below the threshold of AChE inhibition. *However, to our knowledge, very little of this evidence would (so far) suggest that blood levels of chlorpyrifos in the pg/g range would have significant deleterious neurotoxicological effects in a mammalian species. Without any evidence in the animal literature or elsewhere of a mechanism of action that could explain how pg/g levels in blood could impair IQ and/or working memory, there does not appear to be biological plausibility*.

2016 SAP Minutes at 40–41 (emphasis added). Moreover, the 2016 SAP pointed out that effects at these extremely low levels are rarely seen even with the most potent acetylcholinesterase-inhibiting drugs, further challenging the plausibility of EPA's conclusions. *See* 2016 SAP Minutes at 54 ("There is a lack of biological plausibility or animal evidence for how picomolar (pM; 10-12M) cord blood levels of >6.17 pg/g chlorpyrifos (>17.6 pM based on the CCCEH analytical results) can alter working memory and produce neurodevelopmental impairment. The mechanisms for how such potent effects can be produced at these concentrations in vivo are not known and have not been previously described. By comparison, the most potent selective anti-AChE drugs in current clinical use to treat deficits in working memory are known to directly engage brain AChE with inhibitory constants (IC50's) in the range of 20,000 pM (physostigmine) to 600,000 pM (tacrine). In this regard, CPFO, the active metabolite of chlorpyrifos, has an IC50 towards AChE of ~10,000 pM. One is left to speculate on one or more causative mechanisms having potencies more than 1,000-30,000 fold lower than cholinergic

drugs known to alter working memory in patients. These estimates are conservative, since they assume chlorpyrifos levels in cord blood will directly reflect CPFO levels in the developing brain, an assumption that is currently unproven given the challenges in directly measuring the active metabolite CPFO in any tissue after exposure."). Moreover, even assuming there were evidence of effects at below levels that result in 10% RBC ChEI, the more complete citation from the SAP Meeting Minutes shows that the SAP strongly discouraged the application of additional uncertainty factors to account for possible effects at levels below 10% of RBC ChEI: "*[T]the Panel agrees with the Agency that applying additional safety factors to the AChE PoDs to account for a possible noncholinergic mode of action (MOA) would be problematic because of challenges in justifying any particular value for such an adjustment*." *Id.* at 18 (emphasis added).

2. EPA-Required Studies Demonstrate Protectiveness of Cholinesterase Inhibition and No Neurodevelopmental Effects Below Exposures Associated With 10% RBC ChEI.

DAS, as primary registrant of chlorpyrifos, has conducted guideline and GLP-compliant studies that demonstrate that the use of cholinesterase inhibition is health protective and that there are *no neurodevelopmental effects at levels below exposures associated with 10% RBC ChEI*. In the landmark neurodevelopmental study (Maurissen et al. 2000), for example, dams were administered 0.3, 1, or 5 mg/kg/day. Even the lowest dose level administered (0.3 mg/kg/day) resulted in substantial plasma and RBC ChEI, but notably there were no effects on learning or memory in pups at either the 0.3 or 1 mg/kg/day level. This study thus supports the long-held view that ChEI remains a sensitive and protective endpoint for risk assessment.

In addition, to specifically comply with an EPA data requirement and in order to purposely explore low dose effects related to chlorpyrifos exposure, another study (Marty et al. 2012) was conducted for chlorpyrifos. During the repeated dosing part of the study, pups and dams were administered chlorpyrifos at levels of 0, 0.05, 0.1, 0.5, 1.0, and 3.5 mg/kg/day. The lower end of the dose range in this study is substantially lower than those testing regimes in the vast majority of other studies cited by EPA. Results of this study showed that there were no effects on neurobehavior as evaluated through a functional observation battery and motor activity evaluation in the repeat portion of the study in either dams or pups at dose levels that were associated with less than 10% RBC ChEI in both female pups (0.1 mg/kg/day) and dams (0.05

mg/kg/day). Male pups also had no effects associated with functional observation battery or motor activity, but had approximately 14% RBC ChEI at the lowest dose (0.05 mg/kg/day) tested. This study thus provides an example of where neurodevelopmental effects were not observed in in vivo testing at exposures associated with approximately 10% RBC ChEI or lower.

Finally, a review of both EPA and SAP publications and reviews during Registration Review of chlorpyrifos demonstrate that there is little, if any, data from toxicological studies showing that neurodevelopmental effects result from exposure to chlorpyrifos that results in less than 10% RBC ChEI. A complete summary of these publications and reviews is set forth in Appendix D, Summary of Former EPA and SAP Reviews of Robustness of Animal Toxicology Literature for Chlorpyrifos Relative to Existing Regulatory Standard. *See also* Section III, *supra* (summarizing how the regulatory history and toxicology data for chlorpyrifos affirm that the current regulatory standard protects human health).

In summary, EPA is taking unfounded liberties in inferring that there is evidence for adverse health outcomes in toxicology studies associated with chlorpyrifos exposures below levels that result in 10% RBC ChEI.

References:

EPA, Transmittal of Meeting Minutes of the April 19-21, 2016 FIFRA SAP Meeting Held to Consider and Review Scientific Issues Associated with "Chlorpyrifos:Analysis of Biomonitoring Data" (July 20, 2016).

Johnson, F.O., Chambers, J.E., Nail, C.A., et al. 2009. Developmental chlorpyrifos and methyl parathion exposure alters radial-arm maze performance in juvenile and adult rats. Tox. Sci. 109:132-142.

Marty, M.S., Andrus, A.K., Bell, M.P., et al. 2012. Cholinesterase inhibition and toxicokinetics in immature and adult rats after acute or repeated exposures to chlorpyrifos or chlorpyrifos-oxon. Reg Toxicol. Pharmacol. 63:209-224.

Maurissen, J.P.J., Hoberman, A.M., Garman, R.H., et al. 2000. Lack of selective developmental neurotoxicity in rat pups from dams treated by gavage with chlorpyrifos. Tox. Sci. 57:250-263.

EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting held April 10–12, 2012 on Chlorpyrifos Health Effects (July 11, 2012).

EPA, Science Issue Paper: Chlorpyrifos Hazard and Dose Response Characterization (Aug. 21, 2008).

EPA, Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration Review (June 30, 2011).

EPA, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (Dec. 29, 2014).

EPA, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (Nov. 3, 2016).

B. The 2016 SAP's Statement that "[E]pidemiology . . . studies *suggest there is evidence* for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% RBC AChE inhibition" Does Not Demonstrate Causation.

In its 2016 RHHRA, EPA repeatedly refers to the 2016 SAP's statement that "epidemiology . . . studies *suggest there is evidence* for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% RBC AChE inhibition." 2016 RHHRA at 18, 25, 53. EPA implies that this statement is validation for cause and effect between exposure to chlorpyrifos and the neurodevelopmental effects observed in the Columbia cohort, and justifies the Agency's crack and crevice methodology and time weighted average approach. But the Agency has grossly inflated the significance of the SAP's statement. First, it is well-settled that "[e]pidemiology does not measure causation, only association." Dr. Banner Comments at 5. *See also* Dow AgroSciences LLC's Response to EPA Revised Human Health Risk Assessment for Chlorpyrifos Registration Review, EPA-HQ-OPP-2008-0850-0845 at 35 (Apr. 29, 2015) (noting that case law and EPA's own DRAFT Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment have observed that epidemiology studies suffer from deficiencies and do not prove causation). The 2016 SAP was not charged with determining causation, and EPA is simply wrong to rely on the SAP's statement for proof of causation.

Second, EPA takes the SAP's actual statement out of its proper context. EPA fails to note that this statement was made as part of a discussion regarding the numerous concerns the SAP had about using the Columbia study quantitatively for risk assessment purposes. SAP Tr. at 622 ("[O]ther panel members have an opinion that the [Columbia] study, while suggesting a link between prenatal chlorpyrifos exposure and developmental impairments, *is plagued by issues that diminish the enthusiasm for this study and create a host of uncertainties*. The panel agrees that . . . epidemiology . . . studies *suggest* there is . . . evidence for adverse health outcomes

associated with chlorpyrifos exposures below levels that result in 10 percent red blood cell acetylcholinesterase inhibition. However, the panel agrees with the agency that applying additional safety factors to acetylcholinesterase PoD to account for a possible noncholinergic [mode of action] would be problematic because of the challenges in justifying any particular value for such adjustment." (emphasis added)). The context within which the quoted statement was made makes it clear that the SAP did not find a validated causal connection between chlorpyrifos exposures below 10% RBC AChE inhibition and adverse health outcomes. In addition, the SAP's phrases "suggest there is evidence" and "associated with" do not describe causation, and do not mean "definitively shows" or "demonstrates." Indeed, the SAP did not make a causal determination between cord blood measures and neurodevelopmental outcomes. SAP Tr. at 623 ("In other words, cord blood measures of chlorpyrifos *may be associated* with neurodevelopmental outcomes *but not causal*.") (emphasis added). A mere "suggestion" of an "association" implies that further study is warranted and is simply not enough on which to base major, precedent-setting regulatory action.

VI. EPA's Proposed Regulatory Point of Departure for Chlorpyrifos is Based on a Dose Reconstruction Methodology that is Scientifically Flawed, Contrary to the Weight of the Evidence and SAP Recommendations, and for which Scientific Peer Review is Absent, and Violates Due Process.

Ignoring the Columbia study's limitations and the guidance of numerous SAPs, EPA is now advancing a new, theoretical exposure assessment that rests on the Agency's flawed assumption that the Columbia study establishes a causal relationship between chlorpyrifos exposure and neurodevelopmental impacts. EPA is advancing this approach based on the Columbia study findings notwithstanding the 2016 SAP's conclusions that the cord blood data underpinning those findings are unreliable and invalid. In addition, EPA's exposure assessment is based on unsupported and hearsay assumptions about chlorpyrifos use. Specifically, the input values used by the Agency to calculate the PoD were calculated based on an assumed crack and crevice exposure scenario that did not take into account exposure from other routes such as diet or drinking water.

Moreover, contrary to the Agency's suggestion, EPA's new proposal for assessing exposure does not comport with the 2016 SAP's recommendations. It is also contrary to the scientific weight of the evidence, including other epidemiologic research, and the Agency's own recommendation for the integration of epidemiology in risk assessment, as set forth in its 2010

Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment. EPA, Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment (Jan. 7, 2010) ("Draft Framework").

EPA's new exposure assessment is especially problematic because its methodologies and conclusions have not been subjected to independent peer review. As explained above, EPA is proposing to take unprecedented regulatory action on the basis of significant changes in established scientific methods for setting a PoD. In addition to the need for further review of the scientific validity of the Agency's continued reliance on the results from the Columbia study, EPA's proposed approach to setting a new PoD contains several other significant issues that have not been validated or addressed in previous SAPs. EPA's 2016 RHHRA presents yet another unprecedented approach based in significant part on the Columbia study, and as set forth in the request to EPA Administrator Gina McCarthy submitted by thirty-five U.S. agricultural organizations (dated January 12, 2017), the proposed approach demands additional, independent SAP review. *See* Ex. 1.

A. EPA Continues to Improperly Make the Columbia Study the Centerpiece for its Latest Regulatory Approach.

As explained in Section IV.A., above, the 2016 SAP roundly rejected EPA's unprecedented proposal to derive a new PoD for chlorpyrifos based on as yet unseen biomonitoring data from the Columbia study. Panel members uniformly disagreed with basing regulatory action on a single, unreplicated study. *See, e.g.,* SAP Tr. at 534–38, 771–72 (reliance on one study goes "against standard practices of science "and sets a bad precedent"). In addition, Panel members raised concerns about EPA's reliance on a single measure of chlorpyrifos in cord blood to develop a new regulatory standard. The Panel's concerns were consistent with those of several prior SAPs, which deemed the Columbia study insufficient for use quantitatively in risk assessment. *See supra,* Section IV.C.

Rather than address the SAP's recommendations in a scientifically rational way, EPA has instead developed yet another (and even more questionable, non-validated) regulatory proposal in a last ditch effort to salvage the Columbia study as the basis for undermining decades of rigorous toxicology data that support existing health assessments of chlorpyrifos around the world. To be sure, the "scientific evidence" underlying EPA's latest proposal has not changed. EPA has simply developed a new, fictitious exposure assessment in an attempt to sidestep the

SAP's concerns about using a single cord blood measurement quantitatively to derive a PoD. Though EPA claims to be using the Columbia study "qualitatively," *see* 2016 RHHRA at 14, EPA's new analysis is premised on its scientifically unsupported assumption that the Columbia study findings establish a *causal* linkage between neurodevelopmental outcomes and chlorpyrifos exposures below the current regulatory level. *See* 2016 RHHRA at 13 ("EPA's assessment is that the [Columbia study] . . . provides sufficient evidence that there are neurodevelopmental effects occurring at chlorpyrifos exposure levels below that required for AChE inhibition."); *see also* J. Dawson, *Alternative Risk Assessment Approach In the U.S. - Chlorpyrifos*, 4th Fresenius Worker Exposure and Risk Assessment Conference, Mainz Germany, at 14, 15 (Dec. 1, 2016) ("Dawson Presentation") (describing first step in EPA's new "hybrid" approach to determine a PoD as "[c]alculate internal dose *causing* neurodevelopmental effects") (emphasis added). With that assumption in place, the Agency proceeds through dose reconstruction to "calculate" the level of exposure that theoretically must have occurred to the Columbia study cohort to produce the effects purportedly observed.

EPA's exposure assessment, however, rests on ill-conceived assumptions about chlorpyrifos use and thus does not meet the level of scientific rigor required for use in tolerance revocation. *See* FFDCA § 408(b)(2)(D)(i), 21 U.S.C. § 346a(b)(2)(D)(i) (EPA must consider "the validity, completeness, and reliability of the available data from studies of the pesticide" in revoking tolerances). In addition, by resting its dose reconstruction analysis on the fundamental assumption that there is a causal link between chlorpyrifos exposure and neurodevelopmental effects (the so-called "qualitative findings"), EPA is accepting the validity of the Columbia study's published findings (which are based on the heavily criticized methodology using the as yet unseen cord blood data) and thus continues to make improper *quantitative* use of the Columbia study.

Finally, EPA's revised analysis completely glosses over additional noted deficiencies in the Columbia study. In the 2016 RHHRA, EPA acknowledges various "uncertainties" in the epidemiologic research, including "the lack of an established MOA/AOP pathway, the inability to make strong causal linkages, and the unknown window(s) of susceptibility" but goes on to state that "[t]hese uncertainties do not undermine or reduce the confidence in the findings of the

epidemiology studies."[9] 2016 RHHRA at 12. In fact, several prior SAPs have reached the very opposite conclusion, determining that numerous and significant limitations in the study made it inappropriate for use in quantitative risk assessment. *See supra*, Section IV.C

B. EPA's Dose Reconstruction Analysis Rests on Unsupported and Hearsay Assumptions about Chlorpyrifos Use.

To develop a new PoD for risk assessment from internal concentrations of chlorpyrifos, EPA reviewed the registered uses that would have been available to the Columbia study cohort. 2016 RHHRA at 14. EPA then conducted interviews with technical pest advisors responsible for overseeing New York City's housing authority and "determined" that crack and crevice use was the predominant type of application method used at the time of the Columbia Study nearly two decades ago. *Id.* at 14–15. Using methodology from EPA's Standard Operating Procedures (2012 Residential SOPs) for that type of application, EPA estimated a theoretical time-weighted average ("TWA") exposure. Using PBPK modeling not peer reviewed for this particular unprecedented use, EPA then estimated an equivalent internal dose. As set forth below, there are a number of critical issues undermining the credibility of EPA's exposure assessment. For further detailed discussion by Driver, et al. 2017 and the expert examination of the dose reconstruction by CLA see comments submitted to the docket.

1. There is no definitive evidence that crack and crevice applications of chlorpyrifos took place.

The 2016 RHHRA states:

> [I]n the summer of 2016, OPP contacted several professional pesticide applicators working in New York City apartment buildings around the time of the CCCEH cohort. These professional pesticide applicators recalled that the crack and crevice use was the predominant use around 1998-2000 (D. Friedman, Record of Correspondence, 10/2016). Based on this input and the mitigation rationale outlined above [schedule of cancelled uses of other chlorpyrifos residential use products],

[9] This is but one of numerous examples of EPA's unprecedented and tortured use of the term "uncertainties" when it comes to chlorpyrifos. For purposes of EPA risk assessment, "uncertainty" was not intended to be used for a situation in which biological plausibility and causation, for example, cannot be established. Reliance on a study in such a situation represents nothing more than guesswork or, at best, hypothesis generation and the need for further research. Nor is the term "uncertainty" appropriate where the Agency has failed to obtain the raw data underlying a study in order to assess the credibility and replicability of the study. These situations instead amount to deficiencies, weaknesses and flaws in the study and/or the use of the study, seriously limiting or negating its use for purposes of risk assessment.

> the agency has focused on crack and crevice exposures for the 2016 risk assessment.

2016 RHHRA at 15. Thus, EPA is basing its unprecedented regulatory action on the recollection of private pesticide applicators and technical advisors responsible for pest control in New York City's housing authority nearly two decades ago to determine the most likely exposure method.

In fact, only three people from two organizations were interviewed, and the Record of Correspondence lacks transparency because it does not publish the specific questions asked of the applicators. *See* EPA Record of Correspondence, EPA-HQ-OPP-2015-0653-0439. The two employees of Assured Environments, a privately owned pest control company in New York, were asked about the typical residential application method for chlorpyrifos in New York City during the time period from 1997 to 2000. But the Record does not indicate whether the interviewer first established whether chlorpyrifos was regularly used or whether other active ingredients were applied alone or in rotation with chlorpyrifos. Indeed, a review of the Columbia study publications demonstrates that crack and crevice use was not representative of the exposure scenarios reported in the Columbia study. *See, e.g.,* Whyatt, et al., Residential Pesticide Use during Pregnancy among a Cohort of Urban Minority Women (2002) at 510 (observing that sticky traps were the most common method used by a sample of 231 women from the Columbia study); Whyatt, et al., A Biomarker Validation Study of Prenatal Chlorpyrifos Exposure within an Inner-City Cohort during Pregnancy (2009) at 562 (stating that 32% of Columbia Study subjects "reported using baits, gels, and traps only," and that 29% of that sample "reported using one or more of the spray methods (can sprays, sprays by exterminator, and pest bombs) with or without the other methods"). In a second interview, of a former Technical Advisor for Pest Control for the New York City Housing Authority, EPA noted that an integrated pest management approach was employed; this included caulking and rotating chemistries so that not just chlorpyrifos was used. Retreatment occurred after three to four months if necessary.

In addition, EPA's evidence gathering constitutes blatant hearsay and raises a number of fact issues: How accurate is the recollection of the pest advisors? Did they actually work in the buildings occupied by the Columbia cohort and, if so, how often during the relevant period? If not, how can they confirm that crack and crevice was in use in the buildings occupied by the Columbia cohort? What additional information did the pest advisors tell EPA not reported in EPA's summary interview memorandum? In short, it is deeply troubling to DAS that these

tenuous, opaque findings based on *recall* of practices taking place sixteen to nineteen years ago form the basis of the Agency's unprecedented use of crack and crevice application as the exposure scenario for dose reconstruction.

2. Even worst-case estimates of crack and crevice exposure represent a small fraction of total aggregate sources of exposure that the Columbia cohort (and the U.S. population) experienced.

In deriving the PoD, EPA assumed that the primary exposure to the Columbia study cohort was via the dermal route as the result of post-application exposure to possible crack and crevice applications of chlorpyrifos and that it was this exposure that caused the claimed effects. An examination of National Health and Nutrition Examination Survey ("NHANES") biomonitoring data for the same period, however, indicates that the greatest potential exposure to chlorpyrifos was through dietary intake and not through other routes such as post-application exposure following crack and crevice treatment. *See* Driver et al. 2017 for analysis. In fact, the NHANES data supports the conclusion that crack and crevice use constituted approximately 20% of the dose derived from dietary and water sources. To consider post-application exposure to crack and crevice application of chlorpyrifos in isolation is not consistent with the aggregate exposure to dietary and food sources that are even greater than crack and crevice exposures and that occurred on a daily basis (and not on a geometrically reduced level each day as EPA assumed for post-application crack and crevice exposure). *See also* Driver et al. 2017. To then assume that the exposure to chlorpyrifos from the crack and crevice treatment was the cause of these effects, when even those who did not have the applications had basically the same exposures, is not scientifically supported.

3. There are many deficiencies associated with EPA's modeling of crack and crevice exposure.

While DAS agrees that the 2012 Standard Operating Procedures for Residential Exposure ("SOPs") provide the appropriate method to calculate crack and crevice exposure, and agrees that PBPK modeling can be used to provide estimates of daily blood levels from crack and crevice application, the specific crack and crevice scenario exposure estimation methodology employed by the 2016 RHHRA raises questions regarding accuracy, precision, representativeness, and reliability, specifically in the context of deriving a PoD.

Several of EPA's SOP inputs seem to be arbitrary; the appropriateness and reliability of these assumptions are discussed fully by Driver et al. and by CLA. These inputs include the

assumption of 10% dissipation of surface residues per day for chlorpyrifos, which may be exaggerated; the assumption that pregnant women spent two hours per day every day on hard surfaces involving extensive and intense dermal contact; all women were assumed to take a shower daily immediately following contact with the hard surface over a thirty-day interval; and EPA only considered inhalation exposure for a two-hour period and dermal exposures for the remaining thirty days. No other exposures were included (*e.g.*, dietary intake as mentioned above), resulting in a gross under-estimate of internal dose. EPA's assumptions likely underestimated actual exposures and therefore resulted in a PoD that is likely unrealistically low.

4. EPA's PoD is not supported by biomonitoring data.

The 2016 SAP members observed that PBPK modeling "is a valuable tool to interpret the biomonitoring data in circumstances where multiple routes of exposure occur and when based on best available information as inputs." 2016 Minutes at 18. Despite the availability of multiple studies conducted using biomonitoring following crack and crevice application, and also biomonitoring data available from NHANES (which is concordant with EPA's DEEM dietary exposure modeling for the general population), there have been no valid biomonitoring data cited by EPA for the purpose of comparison with the crack and crevice exposure estimate or the PBPK model results. Such comparison would be accepted practice for validation of the modeling.

There are several studies in which biomonitoring was conducted following crack and crevice application; these have been reviewed by Driver et al. 2017. The studies analyzed 3,5,6-trichloropyridinol (TCPy), a metabolite of chlorpyrifos, in the urine of study participants. In order to determine the contribution that post-application exposure has on TCPy concentration in urine it is important to measure the TCPy concentration before crack and crevice exposure to establish the background concentration in urine. The background concentration can then be subtracted from the post-application concentration in urine to calculate the TCPy that is attributed to the crack and crevice post-application exposure. In these biomonitoring studies a crack and crevice internal dose of 0.002 – 0.09 μg/kg/day was reported (Table 1) which is consistent with EPA's calculated dose for just crack and crevice exposure (0.0077 μg/kg/day for first 24 hr or an average of 0.0027 μg/kg/day over thirty days; *see* Driver et al. 2017 for further details). However, and this is a key point, the pre-exposure (background) monitoring values and the total daily exposure (*i.e.*, crack and crevice exposure plus background) in the same volunteers were 100-fold greater than the Agency-calculated values for crack and crevice alone. The

majority of the TCPy measured in urine is likely resulting from exposures from food, which shows that the Agency body burden estimates based on crack and crevice exposure is not realistic. Dose reconstruction should be an aggregate across all routes and potential pathways/sources (food, water, indoor residential and other product uses including public health vector control, etc.).

Table VI.1. Comparison of Crack and Crevice ("C&C") Dose Estimates (extracted from Driver et al. 2017)

Study	**Pre-C&C Treatment (µg/kg/day)**	**C&C Treatment Only (µg/kg/day)**	**Aggregate (µg/kg/day)**	**Notes**
Agency Estimate: EPA, RHHRA 2016	NA	0.006[a]	Unknown	75 kg women
Byrne et al., 1998[b]	0.11-0.87	0.002-0.09	0.46 ± 0.30; (0.2-0.88)[c]	household
Hore et al., 2006 [b]	NA	NA	0.32	children
Hore et al., 2006[d]	0.04-1.6	<0.0-0.92	0.17-1.4	children
Krieger et al., 2001[b]	0.3-2.1	NA	0.8-5.3	household

[a]This is an estimate, using the Agency scenario and PBPK model for 10 days to be consistent with Bryne et al. and Hore et al., who monitored TCPy in urine for 10-11 days post C&C. The value reported in the text, 0.0027 µg/kg/day is over the entire 30-day exposure.
[b] These values are based on urinary elimination of TCPy.
[c] Mean +/- standard deviation; range.
[d] Averages for Days 1-5. Note on average over the first 5 days, peak aggregate is lower than pre-treatment maximum.
NA- not available

In summary, with regard to the dose construction, there is no definitive evidence that crack and crevice applications of chlorpyrifos took place, yet a recollection of practice taking place almost two decades ago forms the basis of the Agency's unprecedented use of crack and crevice application as the exposure scenario for dose reconstruction. Furthermore, even worst-case estimates of crack and crevice exposure represent a small fraction of total aggregate sources of exposure that the Columbia cohort (and the U.S. population) experienced; the aggregate exposure to dietary and food sources are even greater than crack and crevice exposures and these occurred on a daily basis (and not on a geometrically reduced level each day as EPA assumed for post-application crack and crevice exposure). Several of EPA's SOP inputs are arbitrary, and

these assumptions likely underestimated actual exposures and therefore resulted in a PoD that is unrealistically low.

References:

Driver, J., Ross, J., Poet, T., Hastings, K., Burns, C. (2017) Public Comments: Chlorpyrifos Revised Human Health Risk Assessment for Registration Review (EPA's Office of Pesticide Programs, November 3, 2016) Posted on EPA-HQ-OPP-2015-0653)

CLA 2017 Comments Regarding Calculation of the Chlorpyrifos Time Weighted Average Concentration in the Blood. Posted on EPA-HQ-OPP-2015-0653

C. EPA's Latest Methodology Actually Shows No Dose-Response Relationship Between Chlorpyrifos and Neurodevelopmental Outcomes.

Before the 2016 SAP, EPA proposed developing a PoD derived from biomonitoring data from the Columbia study. EPA relied on the Columbia study researchers' division of the study subjects into two groups based on the exposure levels derived from chlorpyrifos levels in cord blood: a "higher" exposure group (>6.17 pg/g) and a "lower" exposure group (<6.17pg.g). Chlorpyrifos Issue Paper at 12. EPA then credited the researchers' findings that there were statistically significant differences in neurodevelopmental outcomes as between the high and lower exposure groups. In other words, EPA concluded that those study subjects exposed to higher amounts of chlorpyrifos had a higher likelihood of adverse neurodevelopmental effects compared to the lower exposure group.

In its present analysis, EPA has calculated a single value (0.004 µg/L) as the TWA blood concentration for all Columbia Study subjects based on crack and crevice application. 2016 RHHRA at 17. Thus, EPA is assuming that neurodevelopmental effects purportedly associated with chlorpyrifos exposure are more likely to occur at levels above 0.004 µg/L. EPA's assessment thus concludes that study subjects received the same dose and is no longer drawing a distinction between "higher" and "lower" exposure groups. But if there is no quantitative difference in exposure between the two groups, there is no dose-response relationship and thus no plausible PoD to derive. The lack of a dose-response relationship indicates that something other than chlorpyrifos was actually responsible for the neurodevelopmental effects observed, further undermining EPA's revised risk assessment.

D. Contrary to EPA's Representation, Its Latest Approach is Not Consistent with the 2016 SAP Recommendations.

EPA states in the 2016 RHHRA that its new proposal is based on the recommendations of the 2016 SAP. In particular, EPA states:

> [T]he SAP stated that, given the absence of a particular key window of exposure for the effects shown in the CCCEH study, the EPA *should use* estimated peak blood concentrations or TWA blood concentrations within the prenatal period as the PoD rather than blood concentrations at delivery. . . . [T]he use of the PBPK model coupled with the typical OPP exposure scenarios to derive PoDs based on TWA blood concentrations, *as recommended by the SAP*, provide the strongest scientific foundation for moving forward in human health risk assessment for chlorpyrifos.

2016 RHHRA at 14 (emphasis added). EPA described this approach as a "hybrid" approach.

EPA's statements about purported SAP support for its new proposal are misleading and inaccurate. The SAP suggested some areas for further analysis and approaches EPA might consider after further investigation, but did not lay down a recipe it was advising the Agency to follow. Indeed, when compared against the SAP members' actual statements during Panel deliberations, it is plain that EPA took liberties with the SAP's recommendations and took a number of their conclusions out of context. For example, during the SAP meeting, with respect to the issue of using a TWA, Panel member Dr. Russell Carr observed as follows:

> The idea that the responses observed, for example, the neurological effects, would be detrimental primarily by the blood level of chlorpyrifos at the time of delivery is not logically supportable. Peak or time weighted averaged concentrations during pregnancy or a portion thereof are more logically supported metrics. Such metrics could, in theory, be back calculated from the blood biomonitoring data using a valid [PBPK] model *if one has data on or can confidently make assumptions about aspects of exposure patterns[,] labor delivery, blood collections and other cofounding variables*. If such computations cannot be made with confidence, then cor[d] blood data should not serve as a basis for quantitative human health risk assessment.

SAP Tr. at 538:2–18 (emphasis added). This appears to be where EPA derived its TWA hybrid approach "recipe." However, Dr. Carr was suggesting that a TWA approach might be a more scientifically sound approach to estimating exposure *if* there were additional data or if assumptions could confidently be derived from exposure patterns, labor and delivery, *and* blood collection. Dr. Carr's recommendation thus assumes that EPA would be developing a TWA blood concentration level based on a plethora of blood-related data (beyond a single point in time measurement) *from the Columbia cohort itself*, not assumptions about chlorpyrifos exposure that

are theoretic and speculative and then applied to the cohort. EPA simply did not come close to following all of the important recommendations or cautions from the SAP.

E. EPA's Approach is Contrary to the Weight of the Evidence, and EPA's Attempt to Support the Columbia Study with Additional Epidemiology is Scientifically Unsound.

EPA's new approach, regardless of how it is characterized, continues to rely principally on a single epidemiology study, and casts aside entirely a complete database of guideline-compliant and GLP-adherent toxicological data demonstrating the safety of EPA's existing regulatory standard. EPA has made an unprecedented shift to an approach in which the benchmark health effect is not specified and for which there is no known mode of action. This is inconsistent with principles of sound science, is contrary to EPA's own draft guidance for the integration of human epidemiology studies in risk assessment, and ignores SAP recommendations. EPA's approach is also unsupported by other epidemiology studies, including newer lines of epidemiologic research not addressed in its 2016 RHHRA.

1. EPA has poorly followed its Draft Framework for integration of epidemiology in risk assessment

In 2010, EPA promulgated its Draft Framework, in which it announced its plans to use a weight of evidence ("WOE") approach to "evaluat[e] epidemiology and human incident data, such that all available data are evaluated and conclusions are made on the preponderance of the information rather than relying on any one study." Draft Framework at 7. EPA's Draft Framework further states that "in the WOE analysis, OPP will use the best available data across multiple lines of evidence and from in vitro, in vivo, and in silico data sources to describe the cascade of events from the exposure source to the ultimate health outcome." *Id.*

EPA has done just the opposite in its current approach, singling out and relying primarily on the Columbia study. EPA's 2016 RHHRA fails to incorporate or consider any of the toxicological data the Agency has relied upon since chlorpyrifos was first registered in the United States—including the toxicological data set the Agency deemed complete and robust as recently as 2014—with no explanation for its sudden departure from this integrated approach.

EPA's 2016 RHHRA is even contrary to comments on the Draft Framework that EPA made as recently as October 2016:

> [Mode of Action] ("MOA") and adverse outcome pathway ("AOP")] provide important concepts in this integrative analysis. Both a MOA and an AOP are based on the premise that an adverse effect caused by exposure to a compound can be described by a series of causally linked biological key events that result in an adverse human health or ecological outcome. One of the key components of the Agency's draft framework is the use the MOA framework /AOP concept as a tool for organizing and integrating information from different sources to inform the causal nature of links observed in both experimental and observational studies.

EPA, Draft "Framework for Incorporating Human Epidemiology & Incident Data in Health Risk Assessment," PPDC Meeting Nov. 3, 2016 – Session 7C, at 1 (Oct. 15, 2016). In EPA's current approach, however, EPA has departed from a PoD based on a known mode of action (cholinesterase inhibition) to one in which the health endpoint is not defined and the mode of action cannot be explained. EPA is simply inferring exposure through the alleged presence of *de minimis* amounts of chlorpyrifos in blood—test results heavily criticized by the 2016 SAP—and has identified no specific endpoint or adverse outcome pathway by which chlorpyrifos putatively affected exposed individuals.

2. EPA has not incorporated the 2010 SAP's recommendations regarding the Draft Framework.

The 2010 SAP charged with reviewing the Draft Framework made multiple recommendations for improvement to the Framework. The 2010 SAP recommended against relying upon epidemiologic studies with weak exposure assessment, even those using biomonitoring. When relying upon short-lived chemicals, the collection should be timed with the period of etiologic relevance. The SAP also suggested that the reviews of epidemiology data incorporate a minimum set of criteria for acceptability, determine if the analytic methods were appropriate, quantify the effects of bias, and include null findings in the assessment. Specifically, the 2010 SAP recommended as follows:

- "For the hypothesis-testing designs, the paramount requirement in environmental epidemiology is a well characterized, quantitative exposure assessment that minimizes exposure measurement error and decreases the likelihood of introducing misclassification in categorical or continuous data analyses. The exposure assessment should be evaluated for accuracy, precision and reliability and should include validation where feasible." EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting [held February 2–4, 2010] on the Draft Framework and Case Studies on Atrazine, Human Incidents, and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment" ("SAP 2010 minutes") at 9 (Apr. 22, 2010).

- "In the interests of transparency, the Panel recommends that the Agency establish a set of criteria for determining the acceptability of epidemiologic studies." *Id.* at 10.

- "Determine whether the assumptions of longitudinal analytic approaches are actually met and that these analytic approaches are used appropriately." *Id.* at 19.

- "[I]t is equally important to stress the need for exposure information sufficient to characterize the time period when the exposure would be likely to have its effect on the outcome of interest. In other words, the timing of exposure may be equally if not more important than the level or duration of exposure.… 'Direct' approaches, such as biomonitoring and personal monitoring, are generally not useful for characterizing prior exposures unless the contaminants of interest are very persistent (*i.e.*, bioaccumulate, long half-lives of excretion)." *Id.* at 22.

- "Methods for assessing the impacts of exposure misclassification bias, selection bias, and confounding bias exist. Inclusion of these in relevant studies should be encouraged." *Id.* at 25.

- "Studies demonstrating no association with a pesticide exposure are equally as informative in WOE analysis as those that do." *Id.* at 32.

Despite these suggestions for more robust and transparent review, EPA continues to rely upon the results of the Columbia study as evidence of neurodevelopmental effects from extremely low chlorpyrifos exposure, without a set of criteria in place for evaluation of the study for risk assessment purposes. Indeed, even the most recent SAP questioned EPA's reliance on epidemiology studies without having in place a scheme for the systematic evaluation of the strength of different studies. *See* SAP Tr. at 767. EPA justifies its reliance on the Columbia study by maintaining that the Columbia study is more robust than other studies because the parent compound was measured in blood rather than the metabolite in urine. However, the *medium* alone is not a sufficient measure of quality or reliability. The timing of collection, the biological half-life, documentation of sample stability, avoidance of sample contamination, and repeated samples are well-established aspects of quality exposure assessment. (LaKind et al. 2014).

3. The hypotheses generated by the Columbia study are not supported by other studies, in particular, the Mt. Sinai and CHAMACOS cohorts.

EPA improperly suggests that the Mt. Sinai and CHAMACOS Studies provide additional support for its new proposal for chlorpyrifos. In particular, EPA's 2016 RHHRA states that "the

agency continues to conclude that the 3 U.S. cohort studies (Columbia, CHAMACOS, and Mt. Sinai) provide the most robust available epidemiological evidence." 2016 RHHRA at 12. The CHAMACOS and Mt. Sinai studies, however, assessed non-specific organophosphate metabolites in maternal urine and did not examine chlorpyrifos specifically. PHHRA at 31.

In addition, multiple published reviews of epidemiologic findings of Columbia, Mt. Sinai, and CHAMACOS describe the evidence as inadequate, inconsistent, and implausible (Eaton et al. 2008; Li et al. 2012; Mink et al. 2012; Needham 2005; Weselak et al. 2007; Zhao et al. 2005). Similarly, the authors of a hypothesis-based weight of evidence analysis of chlorpyrifos concluded that the epidemiologic data were inconsistent between chlorpyrifos exposure and neurodevelopmental toxicity (Prueitt et al. 2011). In an unempirical manner, EPA has selected only adverse associations as evidence of causality but has not equally considered the entire scope (*i.e.*, the negative results) of the available data. When using epidemiologic data for human health risk assessment, null findings cannot be viewed as less important than positive ones. Taken together, the results of these birth cohort studies are conflicting and contradictory and do not implicate chlorpyrifos as a developmental toxicant.

4. EPA has not clearly specified the health outcome that it considered for the point of departure, and the health effects reported in the epidemiology studies are not consistent.

The 2016 SAP members challenged EPA's proposal to use a 2% reduction in working memory as the benchmark health effect for setting a PoD. Panel members raised serious concerns regarding the lack of biological plausibility for how extremely low cord blood concentrations of chlorpyrifos (low parts per trillion) can alter working memory and produce neurodevelopmental impairment, and concluded that the Agency provided insufficient justification to base the PoD upon the cord blood concentrations. EPA has now moved away from reduction in working memory and the benchmark effect is not defined at all. No SAP has ever considered such an approach.

Defining a specific adverse outcome for specific dose level is the hallmark of regulatory risk assessment. Thus, the lack of an age-specific benchmark effect is problematic. In humans, there are multiple neurodevelopmental outcomes and diagnoses from birth to age seven. Some have been evaluated by the investigators from Columbia University, Mt. Sinai, CHAMACOS and others for exposure to chlorpyrifos and/or organophosphate metabolites. However, there is

little cohesiveness across these studies with respect to using the same diagnostic criteria and evaluating the children at the same ages. Further, as mentioned above, the results across studies are not consistent. Even within the Columbia study, the results are not consistent. For example, no statistically significant associations were observed for chlorpyrifos for the Columbia study children at ages one and two, and the outcomes were not evaluated using longitudinal analytic approaches (as recommended by the 2010 SAP). At age three, the reported associations in the Columbia study analyses were stronger for the Bayley Psychomotor Developmental Index than for the Mental Developmental Index, suggesting that the focus should be upon physical, not mental, development. This is inconsistent with the initial EPA proposal to use the IQ Working Memory index (age seven) as the PoD.

5. Newly referenced epidemiology studies do not support neurodevelopment effects from chlorpyrifos exposure *in utero*.

EPA's 2016 RHHRA states:

> [T]he EPA's assessment is that the CCCEH [Columbia] study, with supporting results from the other 2 U.S. cohort studies and the seven additional epidemiological studies reviewed in 2015, provides sufficient evidence that there are neurodevelopmental effects occurring at chlorpyrifos exposure levels below that required for AChE inhibition.

2016 RHHRA at 13.

Findings from newly published studies are both negative and positive and do not contribute sufficiently to the evidence of chlorpyrifos induced neurodevelopmental effects (Bouchard et al. 2010; Fortenberry et al. 2014; Furlong et al. 2014; Guodong et al. 2012; Oulhote and Bouchard 2013; Shelton et al. 2014; Zhang et al. 2014). EPA also failed to acknowledge two other birth cohort studies in three publications (Donauer et al. 2016; Yolton et al. 2013; Cartier et al. 2016) that do *not* support adverse neurodevelopmental outcomes associated with chlorpyrifos exposure. The additional studies are summarized in Table VI.2.

Three of the new studies collected urine postnatally. The findings of these studies that rely upon exposures measured in children should be discussed in the context of other studies of postnatal exposures, such as that of Eskenazi et al. (2007) and Bouchard et al. (2011). Overall, the results of the studies of chlorpyrifos metabolites in children have not suggested an adverse effect. Two of the three studies cited by EPA found no association with urinary DEP (diethyl phosphate, a metabolite of chlorpyrifos and other organophosphates) and health outcomes

studied (Bouchard et al. 2010; Guodong et al. 2012; Oulhote et al. 2013). The CHAMACOS children with higher DEP levels tended to score higher on Bayley and IQ tests (Eskenazi et al. 2007; Bouchard et al. 2011).

Regardless of the findings, positive or negative, the studies newly introduced by EPA have a cross-sectional design. Because the exposure and outcome data were collected at the same time, the onset of disease may have preceded exposure. It is possible that observations of higher urinary concentration of a chlorpyrifos metabolite and disease can be due to behaviors unrelated to etiology but be associated to the health outcome. For example, children with behavioral problems by virtue of these problems may be more active and have greater contact with exposed surfaces and plants. Another example might be that children with well-educated and affluent parents are more likely to be diagnosed with ADHD. These parents might also provide their children a diet that is rich in fruits and vegetables, and with pesticide residues.

The other four studies do not support the Columbia Study findings. Fortenberry et al. (2014) reported no statistically significant adverse findings. Furlong et al. (2014), which is an analysis of the Mt. Sinai cohort, did not report their results for TCPy, which are assumed to also be negative. Shelton et al. (2014) used an unvalidated approach for exposure based upon residence. Zhang et al. (2014) correlated reflexes at day three with urinary DEP but did not report if these conditions were sustained as the infant developed. Consequently, and as summarized in Table VI.2, below, the epidemiology is not at all persuasive as to an association of adverse neurodevelopment due to chlorpyrifos.

a. Bouchard et al. (2010). NHANES study. Urinary DEPs in children were significantly associated with a higher prevalence of the hyperactive/impulsive subtype of ADHD. This study should be interpreted in the context of a cross sectional study of children in which the temporal sequence of exposure and outcome is unknown. **NHANES does not support or refute the Columbia in utero study findings.**
b. Guodong et al. (2012). Shanghai children. No adverse associations were reported for DEP and any developmental quotient score. This study should be interpreted in the context of a cross sectional study of children in which the temporal sequence of exposure and outcome are unknown. **The study of Shanghai children does not support or refute the Columbia in utero study finding.**

c. Oulhote and Bouchard (2013). Canada biomonitoring study. No adverse associations were reported for DEP and any developmental test. The findings are in direct conflict with those of similarly designed Bouchard et al. (2010). This study should be interpreted in the context of a cross sectional study of children in which the temporal sequence of exposure and outcome is unknown. **The Canada biomonitoring study does not support or refute the Columbia in utero study finding.**

d. Fortenberry et al. (2014). ELEMENT study. Fortenberry et al. (2014) reported no statistically significant results for urinary TCPy and any of the psychometric assessments. In the 2015 updated literature review (USEPA, 2015), EPA uses the term "suggestive" but it is unclear how this is used in the context of small sample size, poor precision and small size of the association. Specifically, the results of the ELEMENT study are misrepresented by the term "suggestive" and should be characterized as a null study and directly conflict with the ADHD findings from the Columbia study. **ELEMENT does not support the Columbia Study finding.**

e. Furlong et al. (2014). Mt. Sinai cohort. Prenatal DEP was weakly associated with reciprocal social responsiveness (RSR) among black participants and boys at age seven to nine. No statistically significant associations were found among whites or Hispanics, or among girls. Despite availability of urinary TCPy, no analyses were reported for RSR. Mt. Sinai's race and gender specific results are etiologically unsupported.

f. Zhang et al. (2014). Shenyang, China. Tested infants at three days old with the Neonatal Behavioral Neurological Assessment ("NBNA") and compared with maternal DEP concentrations prior to delivery. Decreased scores were reported and is not inconsistent with findings from CHAMACOS and Mt. Sinai. Testing of infants was not done by the Columbia Study and direct comparison cannot be made. Furthermore, the Columbia Study did not identify any statistically significant adverse results until the child was three years old., which is inconsistent with the Zhang adverse finding at infancy. No further assessment of these children has been reported. **This study does not confirm or refute the Columbia Study findings.**

g. Shelton et al. (2014). Statistically significant odds ratio ("OR") was observed for autism spectrum disorder (ASD) and residing within 1.75 km of the pesticide application (OR = 1.78). However, the ORs were smaller for living closer (OR = 1.57 and OR = 1.66 for 1.25

km and 1.5 km, respectively). Similarly, there was no dose/proximity pattern by time period of the pregnancy. Chlorpyrifos was not statistically associated with developmental delay in any analysis. The authors note that error may be introduced because they assume homogeneity of exposure within each buffer. Information on hours spent in the home or elsewhere was not available. This approach for exposure assessment fails to account for factors related to drift (application equipment, formulation, weather conditions) and presence of the subject during or after the application. **This study has unvalidated exposure assessment and should not be used to confirm or refute the Columbia study.**

Table VI.2. Summary of recent epidemiology studies.

Author, year of publication	Outcomes	Exposure Metric	Design and Discussion
Cross sectional studies (outcome and urine collected at the same time)			
Bouchard, 2010	Diagnostic Interview Schedule for Children IV	Urinary DEPs in child (-) single sample	(-) Cross sectional design Urinary DEPs in children were significantly associated with a higher prevalence of the hyperactive/impulsive subtype of ADHD
Guodong, 2012	Developmental Quotient from the Gesell Developmental Schedules	Urinary DEPs in child (-) single sample	(-) Cross sectional design No adverse associations were reported for DEP and any developmental quotient score.
Oulhote, 2013	Strengths and Difficulties Questionnaire	Urinary DEPs in child (-) single sample	(-) Cross sectional design No adverse associations were reported for DEP and any developmental test.
Case control and prospective studies			
Fortenberry, 2014	Conners' Parental Rating Scales-Revised, Conners' Continuous Performance Test, and Behavior Assessment System for Children-2	Urinary TCPy, prenatal (-) single sample 3 samples (during each trimester) for 21 of 187 participants	(+) Prospective design No statistically significant associations were observed between tertiles of maternal TCPy concentrations and ADHD-related outcomes in children ELEMENT does not support the Columbia study findings.
Furlong, 2014	Reciprocal Social Responsiveness	Urinary DEPs, prenatal (-) single sample	(+) Prospective design (Mt. Sinai cohort) Prenatal DEP associated with RSR among blacks and boys Mt. Sinai's race and gender specific results are etiologically unsupported.
Shelton, 2014	Autism Spectrum Disorder	Pesticide application near maternal residence (-) The use of residential proximity to determine exposure has not been validated	(+) Case control design with confirmed diagnosis. This study has an un-validated exposure assessment and should not be used to confirm or refute the Columbia study
Zhang, 2014	Neonatal Behavioral Neurological Assessment at 3 days	Urinary DEP, prenatal (-) single sample	(+) Prospective design Decreased scores associated with DEP. No assessment reported when child was older. This study does not confirm or refute the Columbia study findings at older ages.
Not reviewed by EPA			
Cartier, 2016	Wechsler Intelligence Scale for Children, 4th edition (WISC-IV)	Urinary DAPs, prenatal Urinary DAPs, child (-) single sample	(+) Prospective design No evidence that prenatal exposure adversely affected cognitive function in 6-year-olds.
Donauer, 2016	Bayley Scales of Infant Development Wechsler Preschool and Primary Scale of Intelligence	Urinary DAP, prenatal (+) Two samples	(+) Prospective design (HOME study) No adverse associations of gestational exposure on and cognition at 1 – 5 years of age.
Yolton, 2013	NICU Network Neurobehavioral Scale at 5 weeks	Urinary DAP, prenatal (+) Two samples	(+) Prospective design No detrimental effects of gestational exposure on neurobehavioral outcomes among young infants were reported.

(-) A weak study domain; (+) a strong study domain

References

EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting on the Draft Framework and Case Studies on Atrazine, Human Incidents, and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment (Apr. 22, 2010).

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F. EPA Must Seek Peer Review of its New, Precedent-Setting Regulatory Standard.

In addition to the numerous scientific and policy issues discussed above, EPA's RHHRA is problematic because its methodologies and conclusions have not been subjected to independent peer review. As explained above, EPA is proposing to take unprecedented regulatory action on the basis of significant changes in established scientific methods for setting a PoD. EPA is proposing a new regulatory endpoint based principally on a single, unreplicated epidemiology study—the Columbia study—for which it lacks underlying raw data. EPA is taking this action despite the concerns of no less than three prior SAPs that weaknesses and deficiencies in the Columbia study render it inappropriate for use in regulatory decision-making, and in disregard of over forty years of toxicological data demonstrating the safety of chlorpyrifos under the current regulatory standard. EPA's 2016 RHHRA presents yet another unprecedented approach based in significant part on the Columbia study and, as set forth in a request to EPA Administrator Gina McCarthy submitted by thirty-five U.S. agricultural organizations (dated January 12, 2017), *see* Exhibit 1, the proposed approach merits additional SAP review.

EPA's proposed approach to setting a new PoD contains several other significant issues that have not been validated or addressed in previous SAPs. In particular, EPA should convene an SAP to examine EPA's estimation of a theoretical TWA exposure based on questionable and hearsay assumptions about chlorpyrifos use, as well as the Agency's use of the PBPK model to estimate an equivalent internal dose from possible exposure associated with a crack and crevice application. These are novel scientific issues that no prior SAP has addressed. Indeed, EPA's sudden shift from reliance on precisely measured exposure doses in animal toxicology studies conducted under Good Laboratory Practices and required for registration, to speculative exposures determined through phone and email surveys, demands SAP review—particularly given the enormous ramifications of EPA's proposed action for U.S. agriculture.

EPA's analysis is premised on its fundamentally inaccurate assumption that, based on the Columbia study, there is a causal linkage between chlorpyrifos exposures below the current regulatory level and effects claimed in the Columbia study. But EPA's 2016 RHHRA acknowledges limitations in the Columbia study, including "the lack of established MOA/AOP pathway, *the inability to make strong causal linkages*, and the unknown window(s) of susceptibility." 2016 RHHRA at 12 (emphasis added). Indeed, no causal linkage has been established, let alone "the [ ] ability to make strong causal linkages." EPA downplays these

issues as mere "uncertainties" that "do not undermine or reduce the confidence in the findings of the epidemiology studies." *Id.* EPA's use of the Columbia study in this manner, in light of the numerous deficiencies and limitations in the study raised by prior SAPs that EPA has not addressed, warrants further independent SAP review.

In addition, proceeding with a final rule to revoke tolerances for chlorpyrifos based on the 2016 RHHRA and in the absence of external peer review would raise significant Due Process concerns. A revocation of pesticide tolerances under FFDCA is tantamount to issuance of a notice of intent to cancel the underlying registration under FIFRA Section 6. *See, e.g.*, 40 C.F.R. 152.112(g) (requiring all necessary tolerances to be issued under FFDCA § 408 as a condition of registration under FIFRA). A pesticide registration is a recognized property right under FIFRA. *See Indus. Safety Equip. Ass'n v. EPA,* 656 F. Supp. 852, 856 (D.D.C. 1987), *aff'd*, 837 F.2d 1115 (D.C. Cir. 1988) ("It is well settled that an agency license can create a protectible [sic] property interest, such that it cannot be revoked without due process of law."); *Reckitt Benckiser, Inc. v. Jackson,* 762 F. Supp. 2d 34, 45 (D.D.C. 2011) ("A FIFRA registration is essentially a license to sell and distribute pesticide products in accordance with the terms of the registration and the statute."); Mem. & Order, *Pesticide Action Network of N. Am. v. EPA,* No. C 08-1814 MHP, at 4 (N.D. Cal. July 8, 2008), ECF No. 43 ("The registrations involved here are essentially government licenses to produce, distribute and sell pesticides . . . [and] therefore constitute property[.]"). FIFRA governs cancellation of pesticide registrations and affords the registrant certain process before a registration may be cancelled. This includes the requirement that EPA convene an SAP to provide comments to the Agency on "the impact on health and the environment" of proposed cancellation actions. FIFRA § 25(d)(1), 7 U.S.C. § 136w(d). Should EPA proceed with tolerance revocation and bypass further peer review, EPA would essentially be making an end-run around FIFRA's requirements, in violation of DAS's Due Process rights.

EPA's own guidance indicates that peer review is appropriate in these circumstances. EPA's Peer Review Handbook states that "external peer review is the *expected procedure*" for "highly influential scientific assessments." EPA Peer Review Handbook, App'x A at A-4 (4th ed. 2015) (emphasis added). Independent peer review is also warranted by EPA's Science Advisory Board. 42 U.S.C. § 4365. Given the enormous ramifications and potentially precedent-setting impact of EPA's proposed revocation of all tolerances for chlorpyrifos—one of the most

widely used pest management products in the world—EPA must convene an SAP to conduct external peer review of its 2016 RHHRA before issuing a final rule.

VII. EPA's Reliance on the Columbia Study Without the Raw Data is Arbitrary and Capricious, Violates Due Process, and Contravenes EPA's Statutory Obligations and Executive Branch Directives.

EPA's reliance on the Columbia study to revoke all tolerances for chlorpyrifos without obtaining and reviewing the underlying raw data is arbitrary and capricious, in violation of the Administrative Procedure Act ("APA"). *See* 5 U.S.C. § 706(2)(A) (instructing courts to hold unlawful and set aside agency action held to be arbitrary and capricious, an abuse of discretion, or not in accordance with the law); *see also Motor Vehicle Mfrs. Ass'n v. Ruckelshaus*, 719 F.2d 1159, 1164 (D.C. Cir. 1983) (agency action arbitrary and capricious if it *fails to examine relevant data*). Without all of the raw data from the Columbia Study, EPA cannot meet its statutory obligations under the FFDCA to properly consider "the validity, completeness, and reliability of the available data from studies of the pesticide." FFDCA § 408(b)(2)(D)(i), 21 U.S.C. § 346a(b)(2)(D)(i). For example, without the underlying data from the Columbia study, results cannot be replicated and are therefore not reliable under the FFDCA. *See also, e.g.,* Dow AgroSciences LLC's Response to EPA Revised Human Health Risk Assessment for Chlorpyrifos Registration Review, EPA-HQ-OPP-2008-0850-0845 at 34–37 (Apr. 29, 2015); Dow AgroSciences LLC's Additional Comments to EPA's Chlorpyrifos Issue Paper, 2016-0062-0123 at 6–7 (Apr. 16, 2016).

A revocation of tolerances without reliable data also raises serious Due Process concerns. DAS is concerned that EPA's use of the Columbia study, for which the Agency lacks supporting data and that is refuted by an abundance of quantitative science, sets a double standard for academic researchers and members of the regulated community. EPA commonly requests raw data from pesticide registrants on studies they submit, and DAS and other registrants routinely provide and maintain such data for Agency review to ensure a thorough, high-quality risk assessment. Not holding federally funded researchers to the same standard creates a glaring inconsistency in light of EPA's stated principles of scientific integrity in regulatory matters and raises serious Due Process concerns with respect to the Agency's revised risk assessment for chlorpyrifos in the absence of the underlying epidemiology data. *See Indus. Safety Equip. Ass'n*, 656 F. Supp. at 865 (agency license can create a protectable property interest that "cannot be

revoked without due process of law"); *Reckitt Benckiser, Inc*., 762 F. Supp. 2d at 45 ("A FIFRA registration is essentially a license to sell and distribute pesticide products").

Several courts have held that an agency must have and make available all of the raw data underlying a study in order to rely on that study for rulemaking, and that such data must be "reliable." *See, e.g., United States v. Nova Scotia Food Prods. Corp.*, 568 F.2d 240, 251 (2d Cir. 1977) (failure to disclose scientific data relied upon by agency in fashioning a proposed rule prevented the agency from considering all "the relevant factors," made the rule procedurally erroneous and therefore invalid); *NRDC v. EPA*, 658 F.3d 200, 218 (2d Cir. 2011) (EPA had acted in an arbitrary and capricious manner by relying on a study that was not "reliable data" to lower the FQPA safety factor); *Endangered Species Comm. of Bldg. Indus. Ass'n v. Babbitt*, 852 F. Supp. 32, 36–38 (D.D.C. 1994), *as amended on reconsideration* (June 16, 1994) (observing that "where an agency relies upon data to come to a rulemaking decision, it generally has an obligation under the APA to provide such data for public inspection[,]" and holding that agency's failure to make data available to interested parties violated the APA). *See also Zero Zone, Inc. v. U.S. Dep't of Energy,* 832 F.3d 654, 670 (7th Cir. 2016) (observing that "[s]everal of our sister circuits have held that among the information that must be revealed for public evaluation are the technical studies and data upon which the agency relied") (internal quotation marks and citation omitted).

In connection with the 2016 SAP, EPA relied on *Coalition of Battery Recyclers Ass'n v. EPA*, 604 F.3d 613 (D.C. Cir. 2010), and *American Trucking Ass'ns v. EPA*, 283 F.3d 355 (D.C. Cir. 2002) for the proposition that it need not obtain the raw data. Both cases are readily distinguishable. In *Coalition for Battery Recyclers*, the petitioners failed to raise the need for the raw data until rebuttal at oral argument, and failed to identify errors that would make reliance on the study at issue arbitrary and capricious. In *American Trucking*, the agency was not relying on a taxpayer funded study to take unprecedented regulatory action in the absence of underlying raw data, nor was there any indication that EPA failed to request and disclose the data in response to a FOIA request pursuant to OMB Circular A-110. In contrast, here, EPA is required to request and disclose the raw data underlying the Columbia study, which was supported by federal funds, in response to numerous FOIA requests submitted by DAS and others (most recently on August 19, 2016), pursuant to OMB Circular A-110, and EPA itself has repeatedly requested the raw data from the Columbia researchers, who have refused to provide them. *See* Appendix C. In

addition, *American Trucking* was decided before the Obama Administration's push for greater data transparency in scientific decision-making.

In addition to being unsupported by case law, EPA's reliance on the Columbia study—to the exclusion of a complete database of toxicological studies and in the absence of supporting raw data—contravenes the Agency's policies of data access and transparency in scientific decision-making. *See* President Obama's Mem. on Scientific Integrity (Mar. 9, 2009) ("[T]here should be transparency in the preparation, identification, and use of scientific . . . information in policymaking."); EPA Administrator Jackson Mem. to EPA Employees (May 9, 2009) ("Our regulatory decisions should include a full explanation of the science issues addressed," including "the data relevant to those issues."). EPA's reliance on the Columbia study without obtaining the underlying raw data also violates OMB Circular A-110, which mandates the public disclosure of data underlying federally funded studies used to develop agency action that has the force and effect of law. Indeed, EPA itself has recognized the importance of the raw data, having requested it from the Columbia researchers on numerous prior occasions. Jan. 25, 2013 Ltr. from S. Bradbury to PANNA and NRDC, (Jan. 25, 2013), *PANNA v. EPA*, No. 14-72794, Ex. 8 at 4 (9th Cir. Sept. 10, 2014) ECF No. 1-2 (Columbia study authors had "declined [EPA's] request to provide" the raw data). Despite the fact that the Study was supported with taxpayer funds, the study's authors have steadfastly refused EPA's requests.

VIII. EPA's Use of a 10X FQPA Safety Factor is Unfounded.

DAS has made it abundantly clear in its prior comments that EPA's increase of the FQPA safety factor from 1X in the Agency's 2011 PHHRA to 10X due to "uncertainty" derived by the Agency on the basis of the Columbia study and other epidemiology studies as well as EPA's shift in policy on chlorpyrifos is not consistent with the FFDCA. *See* Appendix A. Safety factors, including those used to propose tolerance revocation, must be based on valid and reliable data. FFDCA § 408(b)(2)(D), 21 U.S.C. § 346a(b)(2)(D). Uncertainty caused by EPA's failure to obtain the underlying raw data for the Columbia study and other epidemiology studies[10] in order to assess the validity and reliability of these studies is not a basis to apply a 10X safety factor and revoke tolerances. Nor is a shift in Agency regulatory policy justified on this basis.

[10] Epidemiology studies that did not specifically deal with chlorpyrifos are not "studies of the pesticide chemical and pesticide chemical residue[s]" and thus are not relevant in any event to the 2016 RHHRA for chlorpyrifos. FFDCA § 408(b)(2)(D), 21 U.S.C. § 346a(b)(2)(D).

This is especially true when: (a) there is no new data or science since the 2011 PHHRA to warrant this reversal; (b) a scientific weight of evidence review that includes both animal and human data supports the conclusion that chlorpyrifos exposure below the current regulatory standard is not associated with neurodevelopmental effects; and, (c) the current PoD based on RBC ChEI for chlorpyrifos is protective of human health.

Moreover, the 2016 SAP's conclusions regarding the cord blood information reported in the Columbia study actually *support* the PHHRA's determination of a 1X safety factor for chlorpyrifos. By finding that the cord blood test results reported in the Columbia study are not reliable, the SAP essentially negated the conclusions that the Columbia researchers reached on the basis of those test results. Thus, the SAP not only removed any "uncertainty" that could be founded on the Columbia study for risk assessment purposes, but also demonstrated why it is so important for the raw data for studies of this nature to be accessible and carefully reviewed before any regulatory action is proposed, let alone action of such an unprecedented nature.

In its 2016 RHHRA, EPA discloses, for the first time, a new basis for the application of a 10X safety factor. EPA contends that the chlorpyrifos blood level it estimated from the crack and crevice application methodology is likely to be a LOAEL (lowest observed adverse effect level) rather than a NOAEL (no observed adverse effect level), and that it is EPA's policy to apply a 10X safety factor in such situations. However, this approach is simply inapplicable to this situation. The LOAEL/NOAEL applies when there is a defined dose-response relationship. Yet there is no defined dose-response relationship in the 2016 RHHRA's approach to chlorpyrifos, especially now that the Agency has discarded the "high" and "low" exposure group distinction in the Columbia study and applied a single TWA. *See supra*, Section VI.C. EPA's 2016 RHHRA is essentially one where unrealistically "measured" exposures through the inherently faulty approach based on assumptions about crack and crevice applications have generated unmeasured, undefined effects. This is no place for application of a 10X safety factor based on LOAEL/NOAEL (and this is certainly not a basis to change the current regulatory standard for chlorpyrifos).

Moreover, discussion of LOAEL/NOAEL is traditionally reserved for experimental toxicology studies that specifically and purposely involve at least three dose levels, thus allowing for the identification of a no-effect level, a lowest-observed effect level, and a maximum

tolerated dose level. Epidemiology studies by their very nature are not designed to establish and then "test" various dose or exposure levels in humans, and hence, there is no basis for EPA inferring that a particular exposure and concomitant blood level represent a particular "effect level"—in this case a LOAEL from the Columbia study. Furthermore, DAS is not aware of previous EPA actions whereby epidemiological studies were evaluated relative to the determination of LOAEL/NOAELs and therefore this current iteration of a 10X safety factor based on the Columbia study is unprecedented, unreviewed by EPA's SAP or Science Advisory Board, and without any scientific basis or rationale.

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EPA, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (Nov. 3, 2016).

IX. EPA Lacks a Scientific Justification for Setting a 10X Intraspecies Uncertainty Factor.

EPA has retained a 10X Intraspecies Uncertainty Factor based on its initial conclusion that the PBPK model for chlorpyrifos does not adequately address the life-stage of pregnancy. However, DAS has updated the model recently to account for this life-stage, and DAS had this this work peer-reviewed by independent external experts. *See* SciPinion LLC, 2016, attached as Ex. 6. This group concluded that the recent expansion of the model to accommodate important life-stage changes that occur during pregnancy are sufficiently robust and validated to allow its use by the EPA and other regulatory bodies globally for risk assessments involving pregnant

women. As such, EPA should be able to now reduce the intraspecies uncertainty factor for pregnant or women of childbearing age to 4X.

In the 2014 RHHRA, EPA utilized the PBPK model for chlorpyrifos to reduce the intraspecies extrapolation factor from 10x to 4x for the general population, but no reduction was made for the women of childbearing age, as the PBPK model did not incorporate pregnancy at that time.

To investigate the appropriateness of this 4x extrapolation factor for pregnant women, the current PBPK model was expanded to include systemic exposure and cholinesterase effects predictions during all stages of human pregnancy in April 2015 (*Poet* 2015). Monte Carlo analyses were then conducted with this updated PBPK model and the results showed that the 4x extrapolation factor is applicable to pregnant women as well.

In the 2016 Chlorpyrifos Issue Paper (EPA 2016), EPA acknowledges these upgrades to the PBPK model. However, the Agency expresses reservations on the validity of the model, as follows:

> While the modified model reasonably simulated the physiological changes during pregnancy, the model's predictive ability to simulate internal dosimetry of chlorpyrifos cannot be properly evaluated since there are no chlorpyrifos-specific pharmacokinetic data available during pregnancy. **As such, the agency cannot evaluate its predictive capacity and thus, the pregnancy model will not be used for risk assessment at this time.**

Chlorpyrifos Issue Paper at 16 (emphasis in original).

To the contrary, all major physiological parameters in the pregnancy model were based on well-characterized datasets:

- Addition of placenta and fetal compartments, which grow over the course of pregnancy
- Pregnancy specific changes in the slow compartment, fat, and rapid compartments
- Pregnancy specific changes in blood composition
    - Changes in blood composition result in increased blood volume, decreased hematocrit
    - Lipids, triglycerides, and cholesterol increase – leads to changes in partitioning

In addition, the critical chlorpyrifos-specific pharmacokinetic/metabolism parameters in this model were also based on well-measured values:

- The changes in blood:tissue partitioning were based on changes in plasma lipid levels, as well as relative differences in partitioning across gestation, in tissues from both pregnant rat and human donors, as described in *Lowe* et al. (2009).

- Pregnancy-related changes in metabolism were also based on measured values:

    - CYP isoform contributions to overall chlorpyrifos activation to the oxon metabolite or detoxification to TCPy were based on experimental *in vitro* data from human CYP enzymes (*Foxenberg* et al. 2007).

    - Pregnancy-based changes in specific CYP levels were obtained from a variety of literature sources (*Dickmann* and Isoherranen 2013, *Mohamed* 2013, *Pennell* 2003, *Sit* 2008, *Tracy* 2005). These values were utilized to calculate gestational time-dependent metabolic rate constants for CYP metabolism, as per methods described in *Foxenberg* et al. 2011 and overall trends reported by *Abduljalil et al.* 2012.

    - Pregnancy related changes in PON1 activity for oxon metabolite hydrolysis were included in the revised PBPK model, and based on several measured datasets (*Huen* et al. 2010, *Sarandol* et al. 2010, *Smith* et al. 2014).

These important changes are included in the CPF model for pregnancy, built on the life-stage platform so either age-specific parameters or initial body weight-specific parameters can be used as the initial condition at the beginning of gestation. All model additions, changes, mathematical implementations, and model code are included in the Pregnancy PBPK model report, submitted to the US EPA in April 2015 (*Poet* 2015). The predictive function of a PBPK model is based upon the use of realistic anatomical, physiological and biochemical compartments. The CPF model has validated all of these major changes in pregnant women over time. Based on these clarifications, DAS feels that the revised version of the PBPK model is functional for predicting both chlorpyrifos pharmacokinetics and pharmacodynamics over the course of human pregnancy. **Therefore, EPA should utilize the model-derived intraspecies extrapolation factor of 4x for all human life-stages.**

DAS engaged SciPinion (SciPinion, 2016) to recruit a panel of experts to review the PBPK model for its appropriateness in evaluation of the life-stage during pregnancy. Results of the peer review revealed the following:

- The entire panel agreed that (a) the physiological and biochemical underpinnings of the model permit their use to effects for which data may not be available (e.g., chlorpyrifos blood concentrations and cholinesterase inhibition in pregnant women) and (b) that key changes in physiology during pregnancy are accurately reflected and appropriately incorporated into the latest revisions of the life-stage PBPK/PD model.

- In the opinion of a majority (a) important chlorpyrifos-specific parameters (e.g., interindividual enzyme activity) and (b) inter-individual variation in sensitivity and the use of advance modeling techniques to evaluate pregnant women have been incorporated into the model.

- Importantly, a majority of the panel agreed that model predictions of chlorpyrifos exposure and effects in pregnant women are as well-developed and validated as other PBPK models that have been used for regulatory risk assessment.

Peer Review of Physiological Based Pharmacokinetic/Pharmacodynamic (PBPK) Model for Chlorpyrifos (Nov. 1, 2016).

Results of this independent peer review of the PBPK/PD model for chlorpyrifos indicate that the recent expansion of the model to accommodate important life-stage changes that occur during pregnancy are sufficiently robust and validated to allow its use by the EPA and other regulatory bodies globally for risk assessments involving pregnant women.

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X. EPA's Use of An Inappropriate PoD Results in Unrealistic Estimates of Risk that Have No Basis in Fact.

EPA's generation of a TWA blood level based on flawed assumptions about alleged crack and crevice chlorpyrifos use nearly two decades ago and an epidemiology study the SAP has deemed unreliable has culminated in an unfounded estimate of risk for all populations and exposure scenarios.

Dietary exposure calculations have remained very steady over the years; DAS agrees with the Agency's highly refined dietary exposure assessments. It is the change in the PoD that has resulted in an implausible estimated dietary risk. Additionally, the inappropriate application of an FQPA safety factor to occupational risk assessment leads to an overestimate of risk and

departs from the FFDCA's statutory text and intent. EPA's new residential post-application and bystander risk assessments also lack plausibility/reasonableness. DAS concurs with the residential post-application exposure assessment presented in the 2014 RHHRA, which concluded that there were no risks of concern. EPA used these same exposures in the 2016 RHHRA, but this time in tandem with the inappropriate PoDs and LOCs. As a consequence, the 2016 assessment overestimated risk and improperly concluded that all residential risks assessed with the updated PBPK-derived PoDs are of concern. Similarly, the 2016 RHHRA grossly overestimated bystander risk. In doing so, EPA ignored studies described by the Agency in 2014 as "high-quality nose-only vapor phase [AChE inhibition] inhalation toxicity studies" 2014 RHHRA at 83-84. These studies demonstrated that no toxicity (*i.e.*, no hazard) occurred at even the maximum achievable inhalation dose (saturation concentration), and based on these studies, the Agency concluded in the 2014 RHHA that there was no risk potential to bystanders. DAS concurs with the 2014 RHHRA that there are no anticipated risks of concern from exposure due to the volatilization of either chlorpyrifos or chlorpyrifos oxon, but vigorously disagrees with EPA's use of the inappropriate PoD methodology in its 2016 RHHRA.

A. EPA's Dietary Risk Estimates Lack Plausibility/Reasonableness.

Dietary exposure calculations have remained very steady over the years; DAS agrees with the Agency's highly refined dietary exposure assessments. It is the change in the PoD based on the Agency's inappropriate reliance on the Columbia study and flawed exposure assessment that has resulted in a highly unrealistic estimated dietary risk. Table X.1 illustrates the steady exposure from food over the course of EPA's recent review of chlorpyrifos for two example sub-populations. The Table illustrates the dramatic shift in EPA's assessment and highlights how the application of EPA's new methodology to derive a new point of departure unrealistically estimates risk.

The Table also shows that the new PoD (based on post-application crack and crevice exposure) was selected because it is much lower than the food exposure and thus yields an even lower acceptable dose.

Table X.1. Chronic and Steady State Dietary (Food Only) Exposure and Risk Estimates for Chlorpyrifos

Year/document	PoD (µg/kg/day)	PAD (µg/kg/day)	Food exposure (µg/kg/day)	Exposure as % of PAD
Children 1-2 yrs				
2011 Preliminary HHA	30 ($BMDL_{10}$)[a]	0.3 (cPAD)	0.025	8.4
2014 Revised HHA	99 (ssPoD) [a]	2.5 (ssPAD)	0.242	9.7
2015 Proposed Rule	99 (ssPoD) [a]	2.5 (ssPAD)	0.242	9.7
2016 Revised HHA	0.17 (ssPoD)[b]	0.0017 (ssPAD)	0.242	14,000
Adults (Females 13-49 yrs)				
2011 Preliminary HHA	30 ($BMDL_{10}$)[a]	0.3 (cPAD)	0.007	2.2
2014 Revised HHA	78 (ssPoD)[a]	0.78 (ssPAD)	0.075	9.6
2015 Proposed Rule	78 (ssPoD)[a]	0.78 (ssPAD)	0.075	9.6
2016 Revised HHA	0.12 (ssPoD)[b]	0.0012 (ssPAD)	0.075	6,200

$BMDL_{10}$= benchmark dose lower confidence limit for 10% RBC ChE inhibition
[a] PoD based on 10% RBC ChE inhibition
[b] PoD predicted by PBPK modeling of dietary exposure that would produce TWA of chlorpyrifos in blood of 0.004 µg/L (concentration predicted from crack and crevice exposure and implied to be associated with neurological effects)

B. EPA Has Inappropriately Applied an FQPA Safety Factor to Occupational Risk Assessment.

Occupational exposure does not fall under the ambit of the FFDCA, and therefore the 10X FQPA safety factor applied (inappropriately) to dietary exposures should not be applied to occupational exposure assessment. The EPA's proposed approach to chlorpyrifos continues a troubling trend by the Agency to depart from the carefully crafted provisions of FFDCA Section 408, as amended by the FQPA. As a case in point, Congress established the standard that EPA must use when establishing or leaving a tolerance in effect for a pesticide chemical residue. That standard requires that "the tolerance [must be] safe." FFDCA § 408(b)(2)(A)(i), 21 U.S.C. § 346a(b)(2)(A)(i).

> The term "safe" means that EPA has determined that:
>
> there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.

FFDCA § 408(b)(2)(A)(ii), 21 U.S.C. § 346a(b)(2)(A)(ii) (emphasis added). And Congress went on to define the term "pesticide chemical residue" to mean:

a residue in or on raw agricultural commodity or processed food of—

(A) a pesticide chemical; or

(B) any other added substance that is present on or in the commodity or food primarily as a result of the metabolism or other degradation of a pesticide chemical.

FFDCA § 201(q)(2), 21 U.S.C. § 321(q)(2) (emphasis added).

Based on the literal language of the FFDCA Section 408, aggregate exposure under the general safety standard applies to the "pesticide chemical residue"—*i.e.*, a residue "in or on food." EPA's attempt to shoehorn occupational exposure (and drinking water) into this standard raises serious legal and policy issues.

Further support for limiting the safety standard to pesticide chemical residues in or on food can be found in the companion amendments made to FIFRA by FQPA. Specifically, the definition of the pesticide registration standard was amended so that "a *human dietary risk* from residues that result from a use of a pesticide *in or on any food* inconsistent with the [safety] standard under section [408]" triggers a cancellation action for the relevant food uses of that pesticide. FIFRA § 2(bb), 7 U.S.C. § 136(bb) (emphasis added).

Based on the foregoing, the total uncertainty factor (UF) for occupational exposure in the 2016 RHHRA should be 10X and not 100X. Consequently, the Level of Concern (LOC) should be 10 and not 100.

Additionally, as was noted above for dietary exposure, chlorpyrifos exposure from the majority of occupational scenarios has remained steady over time because exposure is calculated using inputs from long-established exposure databases and methodology. Once again it is the new PoD that has resulted in the enormous differences in estimated risks for operators presented in the 2016 RHHRA's Appendix F compared to previous risk assessments. The impact of the new PoD combined with the inappropriate addition of the FQPA safety factor results in dramatically different occupational MOEs compared to those from previous risk assessments.

C. EPA's Residential Post-Application Risk Assessment Lacks Plausibility/Reasonableness.

DAS concurs with the residential post-application exposure assessment presented in the 2014 RHHRA, which concluded that there were no risks of concern. EPA used these same estimated exposures in the 2016 RHHRA, but this time in tandem with the updated and improperly derived PoDs and LOCs. Not surprisingly, as a result the 2016 RHHRA inappropriately concludes that all residential risks assessed with the updated PBPK-derived PoDs

based on alleged crack and crevice uses of chlorpyrifos during the time of the Columbia cohort are of concern.

D. EPA's Bystander Risk Assessment Lacks Plausibility/Reasonableness.

As set forth repeatedly herein, the PBPK-derived PoD based on alleged crack and crevice uses of chlorpyrifos during the time of the Columbia cohort is unrepresentative, unreliable and inappropriate for risk assessment. Use of the new improperly derived PoD leads to a dramatic departure from EPA's previous conclusions which were based on a wealth of robust, science-based data including a new study conducted specifically to address the risk from inhalation of chlorpyrifos.

The 2014 RHHRA comprehensively assessed the risk to bystanders via spray drift and volatilization and DAS concurs with the conclusions the Agency reached at that time that: (i) there are no anticipated risks of concern from exposure due to the volatilization of either chlorpyrifos or chlorpyrifos oxon; and, (ii) buffers of zero to twenty-five feet are protective of both adults and children 1 to <2 years old who may be exposed as a result of drift from treated fields.

The history of recent risk assessment for exposure to bystanders from spray drift is summarized by EPA in the 2016 RHHRA:

> The potential risks from spray drift and the impact of potential risk reduction measures were assessed in July 2012 (J. Dawson et al., D399483, 07/13/2012). This evaluation supplemented the 2011 assessment where limited monitoring data indicate risks to bystanders. To increase protection for children and bystanders, chlorpyrifos technical registrants voluntarily agreed to lower application rates and to other spray drift mitigation measures.

2016 RHHRA at 30.

Spray drift mitigation measures and use restrictions have been in place on all chlorpyrifos agricultural labels since December 2012. In the 2014 RHHRA the Agency evaluated adult and children 1 to <2 years old spray drift buffer zones for aerial, groundboom and airblast applications and using several nozzle droplet types. Utilizing the PBPK-PD model, the Agency completed an updated assessment based on the PoD of 10% RBC AChE. DAS supports the Agency and the science-based decision using PBPK and the appropriate PoD, and agrees with the Agency conclusion indicating that buffers of zero to twenty-five feet are protective of both adults and children 1 to <2 years old who may be exposed as a result of drift from treated fields.

As such, buffer restrictions on product labels should be revised to reflect the conclusions of the 2014 risk assessment.

With regard to the risk from post-application inhalation exposure (from volatilization) the Agency conducted a preliminary assessment in 2013 that "indicated that offsite concentrations of chlorpyrifos and chlorpyrifos-oxon may exceed the target concentration based on the toxicological endpoints used at the time." 2016 RHHRA at 31. In response to this assessment, DAS conducted two inhalation studies for both chlorpyrifos and chlorpyrifos-oxon which were reviewed by EPA in the 2014 RHHRA as part of a re-evaluation of the 2013 preliminary assessment. The Agency described the studies as "high quality nose-only vapor phase inhalation toxicity studies." 2014 RHHRA at 83–84. These studies demonstrated that no toxicity (*i.e.*, no hazard) occurred at even the maximum achievable inhalation dose (saturation concentration), and the Agency concluded that there was no risk potential, as risk is a function of both exposure and hazard. *Id.* at 84.

DAS concurs with the 2014 RHHRA that there are no anticipated risks of concern from exposure due to the volatilization of either chlorpyrifos or chlorpyrifos oxon, but DAS is very concerned that EPA essentially ignored these studies for purposes of the 2016 RHHRA.

XI. EPA Is Relying on a Flawed Drinking Water Modeling Analysis.

A. Introduction

To calculate the potential for human exposure to pesticides through drinking water, EPA relies upon computer simulations. The Agency bills the updated drinking water assessment for chlorpyrifos (Bohaty and Hetrick, 2016; docket reference EPA-HQ-OPP-2015-0653-0437) as a highly-refined and final assessment and appropriate for use in a refined aggregate human health risk assessment. However, the assessment is inadequate for this purpose, as it is merely a slightly modified screening-level assessment. The input parameterization of the modeling consists of a series of compounding conservative factors and does not employ readily-available data and well-understood methodologies for defensible and straight-forward refinements that would much more realistically reflect the potential for human exposure.

The Agency clearly states, and DAS concurs, that the intensity of the use of a product will be a major determining factor in the magnitude of the potential residues in surface water bodies. However, EPA did not factor this concept into its assessment for chlorpyrifos. Instead,

EPA speculated that since a drinking water catchment *could contain* a high intensity of agriculture, then the Agency's assumption of treatment of an entire watershed, at the maximum labeled use rate, on the same day, was justified. The Agency further justified its assumptions by citing wide-area (non-crop) uses of chlorpyrifos; but most of these uses are no longer supported by DAS and even if occurred to parts of the watershed would likely not have occurred with the same timing and use pattern as any crop applications. The Agency claimed that its modeling was validated by comparison to monitoring data, when scaled to account for sampling bias. This comparison is at best of limited scientific validity.

As it stands, EPA's purported refined and final assessment is neither, as a lack of refined modeling, spatial reference and detail limits its utility for risk assessment. The Agency has ignored DAS's submissions and offers to collaborate on methodologies to refine the assessment, and has thus missed the opportunity to leverage these data and other information to advance the understanding of the potential impact of chlorpyrifos upon surface water resources.

EPA is basing the assessment of risk through drinking water using approaches which are outdated and fail to implement the most current and available methodology. Refinement methodologies have been provided to EPA but are not included in the current assessment. EPA should bring these proposed refinement techniques to a SAP and seek guidance on how to make the Agency's assessments reflect the latest, best science before using an approach that was last reviewed eighteen years ago. In addition, EPA continues to rely on worst-case scenarios for key refinement parameters. The impact of such worst-case assumptions and guidance on how to determine and utilize more realistic assumptions should be addressed by a SAP. It is for these reasons that thirty-five U.S. agricultural organizations submitted a letter to Gina McCarthy, Administrator, U.S. EPA (dated January 12, 2017), requesting that EPA convene a SAP to consider EPA's approach and methodology used in the drinking water assessment for chlorpyrifos. *See* Ex. 1.

B. EPA's Current Drinking Water Assessment Is Not Highly Refined and Is Incomplete.

EPA describes its current drinking water assessment as "highly refined." This is an incorrect characterization, as the work is little more than a slightly modified screening-level assessment. This is primarily due to the overriding assumption that the entire area of any drinking water catchment where chlorpyrifos is labeled for use will receive applications on the

same day, at the maximum use rate, with additional applications occurring at the shortest labeled retreatment interval. This, in conjunction with an exposure model parameterized to reflect a highly-vulnerable watershed, along with other conservative assumptions, leads to extreme estimates of potential drinking water concentrations that are not reflective of the real-world use of the product.

The Agency clearly states, and DAS concurs, that the intensity of the use of a product will be a major determining factor in the magnitude of the potential residues in water bodies. A well-accepted way of reflecting the intensity of use is through the use of Percent Cropped Area ("PCA"), which are adjustment factors representing the fraction of a catchment covered by a given land cover or treated crop. Modeled Estimated Drinking Water Concentrations ("EDWC") for each crop in the catchment are then simply multiplied by the corresponding PCA and the results summed to give an adjusted EDWC.

In previous guidance (USEPA, 2014), EPA described methodology for defining PCA factors for a nationwide set of community water systems ("CWS") for some major crops. The drinking water intakes and corresponding watersheds in this guidance (the "CWS-DWI" dataset)[11] are based upon a 2012 extraction of data from EPA's Office of Water comprehensive Safe Drinking Water Information System ("SDWIS"). In the current drinking water assessment for chlorpyrifos, EPA discusses the CWS-DWI dataset in some detail and states that "there are a lot of data that can be utilized in deriving exposure estimates based on the CWS DWI PCA" Drinking Water Assessment at 63, but EPA recommends a PCA of 1 because of "the extent of chlorpyrifos uses including adult mosquito control, golf course turf, and general wide area use" Drinking Water Assessment at 88. However, such uses are not supported by DAS and thus the Agency's statement that "[i]f the chlorpyrifos use profile changes, the data are provided to easily facilitate investigation of the potential exposure without having to update this assessment," i*d.* at 64, is indeed applicable and further refinement by application of appropriate PCAs should be undertaken.

The Agency further insists on a PCA of 1 (*i.e.*, the entire watershed contains the crop under evaluation) because of a perceived lack of reliable data for some agricultural and vegetable

[11] It should be noted that registrants do not have access to these data, due to Department of Homeland Security restrictions.

crops. However, there are high-quality and readily accessible data available - the USDA Cropland Data Layer ("CDL"), for example. It should be noted that the 2014 CWS PCA Guidance indicates that the use of the CDL in place of the less detailed NLCD data "will be considered for future analysis" to update the CWS-DWI PCA values. The Agency has considerable experience with the CDL, and has defined it as "Best Available Data" in the Endangered Species Act context for defining potential product use areas (USEPA, 2016). In addition, MRID 50016001 (submitted by DAS to the Agency) offers a grouping technique to account for some of the uncertainties in vegetable classes which merits consideration.

The Agency additionally postulates that PCA refinement is not possible because of the possibility of small drinking water watersheds with high agricultural intensity, and recommends that the CWS-DWI dataset "be used to identify areas where exposure concentrations are expected to be higher" and further that "HUC-12 watersheds could be used as a surrogate … where watersheds were not delineated." Drinking Water Assessment at 63. However, the Agency goes on to say that with such an approach "the exposure could be underestimated," *Id*., since some of the specific CWS-DWI catchments and intakes may have changed over time; EPA also notes that some drinking water catchments might be smaller than HUC-12s and, thus, that the surrogates may be underpredictive. Changes in intakes or catchments no doubt happen, but they do not completely negate the usefulness of the CWS-DWI—there is no reason to believe that the overall distributions of surface water source drainage catchment sizes and populations, for example, would have changed drastically in a few years' time. These issues clearly point to the need for further analysis to identify specific areas with higher exposure potential for true drinking water watersheds, such as the concepts discussed in the September 2015 meeting with EFED (summarized in EPA-HQ-OPP-2008-0850-0853) (September 2015 EPA Meeting"), as well as the approach presented in DAS's Preliminary Refined Drinking Water Assessment (MRID 50016001), submitted in February 2016.

The data used in generating Figure 10 of the EPA assessment and the discussion preceding it highlight some of the refinement opportunities if the CWS-DWI database were to be more fully utilized. Drinking Water Assessment at 56-60. In addition to DA to NC ratios or field size to surface area ratios that can be evaluated (these are fixed in the Index Reservoir ("IR") modeling framework), the data would allow for testing of assumptions, for example, of vulnerable soils and drainage area to waterbody ratios for actual watersheds to determine when

the IR is a good surrogate or when refinements are required. The data would allow the Agency to make progress in identifying modeling frameworks that would better represent actual conditions. The assumptions of treatment on same day, relatively stagnant reservoir and simple direct drift to contributing water load can all be evaluated and refined with the data available to the Agency. Inclusion of flowing system hydrology, particularly when considering 21-day concentrations, is critical in identifying areas of concern.

The current EPA drinking water assessment claims to perform regional refinement of the exposure potential of chlorpyrifos. This was done, albeit superficially, by reflecting regional/state labeling restrictions in the modeling and using the CDL and USDA Census of Agriculture data to determine whether a certain crop is indeed grown within a given HUC-2. The assessment still relies upon the long-established set of standard soil/cropping/weather scenarios parameterized within the IR framework for use in the Pesticides in Water Calculator ("PWC") model, with some minor modifications. The IR conceptual model itself is an extreme case. As described in comments to the 2014 assessment (Reiss, 2015), although the Agency has appropriately characterized the IR drainage as a 90th percentile case based on a Drainage Area to Normal Capacity ratio (Jones et al. 1998), additional assumptions render the scenario non-representative of real-world conditions.

If a model input scenario for a crop of interest did not spatially exist in the HUC-2 of interest, "surrogate scenarios" for the simulated crop groups were selected from an adjacent HUC-2, parameterized with the highest runoff curve number, as representative of the highest runoff potential. This approach would not necessarily select the scenario with the highest runoff, as the runoff is also a function of the rainfall intensity and timing in relation to chemical application events. EPA's methodology is similar to the approach employed in the DAS submission of Feb 2016 (MRID 50016001); that submission also included the building of additional scenarios, if none were available in a given or adjacent HUC-02.

In selecting weather scenarios for the surrogates, the Agency selected the SAMSON weather station within the HUC-02 with the median 30-year total rainfall as representative. When a large range was seen in the total rainfall, some HUC-02s were divided into a low and high group (i.e., two weather scenarios were simulated). It is not known if this approach over- or under-estimates runoff for a given soil/crop scenario. Given the large spatial extent of the HUC-

02's and factors such as elevation and coastal effects, a more science-based approach would be to select weather scenarios on a more spatially-specific basis, such as was done in DAS's submission (MRID 50016001). Even this would still be, in actuality, a screening-level assessment. A much deeper understanding of the potential exposure risk could be explored with readily available spatial data. For example, more spatially-relevant scenarios could be developed by using CDL data on cropping, overlapped with the specific soils data (SSURGO, for example) along with detailed historical weather data. Such spatially-specific approaches have been presented by industry in the past. Indeed, similar concepts under development by the Agency in the new SAM model framework offer an opportunity to move beyond the scenario-based approach, and work to identify actual areas of greater or lesser vulnerability within the agricultural landscape.

EPA endeavored to explore the relative contributions of other modeling input parameters to the EDWCs via a limited sensitivity analysis. The Agency concluded from this effort that changes in environmental fate parameters, runoff curve numbers and application dates "are not expected to alter the risk assessment conclusions." The basis of this conclusion was not a statistical evaluation of sensitivity, but merely observations of the magnitude of modeled output changes resulting from using the bounds of input parameters. In addition, only one parameter was varied at a time, which neglects any interaction between the variables. From these observations, EPA concluded that changes of two- to three-fold were insignificant. However, depending upon the hazard endpoint used in the risk assessment, such changes may indeed be significant and should not be discounted out of hand.

EPA demonstrated a similar mindset through the continued use of absolute maximum application rates and minimum repeat intervals for the simulations, which can have a very significant impact upon the modeled results. In the context of a refined assessment, as EPA represented its effort to be, the use of more typical (and even regionally-dependent) application rates should have been explored. Such an analysis has been performed previously, for example in the work of Soloman et al. (2014).

C. EPA's Drinking Water Assessment Results Are Not Useful for Decision-Making and Do Not Reflect Real-World Observations.

The results of EPA's regional exposure modeling are presented as ranges of EDWC values by HUC-2 and the results of the individual crop simulations are available from the docket.

Since all of the simulations assume a PCA of 1 (the entire cropped area is planted in that crop and treated), within an indeterminate, extremely vulnerable catchment, it is unclear how the results would be used in a refined aggregate human health assessment to realistically reflect the overall use of the product. At this still-screening level, such results are only useful in the most basic exceedance context or to identify uses that may be of particular concern, since the results lack any spatial reference beyond the very large HUC-2 regions (the smallest in the Continental U.S. is about 41,000 square miles in area). If modeled results are to be used for quantitative purposes, modeling must be examined in a more spatially-explicit context, incorporating a more realistic representation of product use, and hopefully of the landscapes of actual drinking water catchments themselves. As was noted previously, such interpretations can also serve to direct further investigations of local conditions and the potential need for locally-specific management or to identify monitoring locations.

In its examination of the monitoring data available for chlorpyrifos, the Agency presents analyses of fifteen chlorpyrifos and five chlorpyrifos-oxon datasets collected within the United States. The fifteen chlorpyrifos datasets can be divided into two categories: those with full every-day sampling (one dataset) and those with incomplete daily sampling (fifteen datasets). All chlorpyrifos-oxon datasets have incomplete sampling.

The dataset with full every-day sampling was collected by the registrant at Orestimba Creek, CA and includes measurements at three sites on the creek. This dataset is also the only targeted monitoring dataset for chlorpyrifos identified in the assessment. Drinking Water Assessment at 90. Because daily sampling was used, both the 1-day and 21-day max can be calculated without interpolation of non-sampled days at each site-year. Since the three sites are on the same water system, the readings are positively correlated across the site-years, suggesting that the data are effectively one site, of little use for a national evaluation. Because of this, these data are ultimately of more use for model evaluation and method development. This was done in the Agency's analysis, which clearly showed the importance of reflecting the use intensity in a catchment, because when approximate PCAs were used in a more detailed modeling representation of the Orestimba, the Agency concluded "[t]herefore, it is expected that the model estimated chlorpyrifos concentrations provide a reasonable upper bound of concentrations that may occur in the environment based on the modeled use and PCA applied." Drinking Water Assessment at 118 (emphasis added).

For the other monitoring datasets, the calculation of time-weighted average concentrations for exposure assessment are complicated by the numerous non-detect samples (censored data) and by the many non-sampled days with no concentration readings.

Many statistical methods are available to adjust for the impact of data censoring on an analysis (Hensel, 2005). The extensive non-detections present with chlorpyrifos require considerable effort to defend a particular method or substitution value. Chlorpyrifos monitoring data are characterized by substantial censoring, causing the ½ LOD substitution used in the analyses of pages 98-113 of the Drinking Water Assessment to have a high degree of influence on the calculations. A more complete approach would be to generate the estimates as a bounding exercise, providing a lower bound analysis with zero substitution, and an upper bound with LOD substitution. This is especially important given the presence of sometimes large lab-specific LODs. As noted in the assessment, these large limits sometimes provide the largest yearly maxima and yet true values are most likely much less. If necessary, large lab-specific values can be subject to a separate sensitivity analysis; an example is shown in Mosquin et al. (2015).

The presence of non-sampled days introduces uncertainty in estimation and also estimation bias for some approaches and target quantities. Estimation uncertainty increases with the number of non-sampled days. Estimation bias can be large for the yearly maximum, which is estimated as the maximum in the sample, which in turn can be no larger than the true maximum over all days. Bias is less of a problem for the maximum 21-day rolling average, since as duration increases the bias decreases. The EPA Refined Drinking Water Assessment attempted to use bias factors to adjust for both uncertainty and bias.

Better methods exist for estimation than bias factors, including multiplicative factors and model-based approaches such as kriging and time series. These methods can also be modified to allow for protective values to be calculated. The bias factor depends on the sampling design, and for a given target quantity, its value increases as the sampling frequency decreases. For a given decision boundary (such as a DWLOC) the proportion of bias factor adjusted values exceeding that boundary will increase as the sampling frequency decreases. That is, the false positive rate goes up as the sampling frequency goes down. Furthermore, a bias-factor adjusted value, if presented on its own, does not give any information regarding the sampling frequency. For heavily censored data, such as those used for chlorpyrifos, bias factors should only be calculated

from site-years where the value of the bias factor is not affected by censoring assumptions, as there will be additional uncertainty added due to the censoring. For this reason, many of the site-years used in Table 69, Drinking Water Assessment at 115 to calculate bias factors are not suitable for that purpose.

The Agency also executed a modeled evaluation of chlorpyrifos with the WARP-MP model (Stone et al. 2013) and found the range of results to "reasonably compare" to the modeled output from the PWC model. However, this is not a fair comparison, because WARP-MP is modeling concentrations in streams while PWC is modeling a vulnerable static municipal reservoir.

EPA further states that the outputs from WARP-MP are representative because "estimated concentrations are derived based on monitoring data and as such reflect actual use data." Drinking Water Assessment at 114. This is incorrect. Data for chlorpyrifos were not included in the development and evaluation data sets of WARP-MP (see Table 1 in Stone et al.). The WARP-MP model uses the WARP model as its base, but with an adjustment factor (the Surface Water Mobility Index or "SWMI" (Chen et al. 2002)) based on chemical properties of a pesticide in question. Thus, WARP-MP was used to model chlorpyrifos concentrations by applying the adjustment factor for chlorpyrifos. There are additional issues with applying WARP-MP for quantitative exposure assessment and the WARP-MP developers recommend that the model is only appropriate for screening to identify high-risk watersheds and guiding targeted monitoring.

The Agency further claims that its modeling outputs are reliable because the results are within an order of magnitude of the surface water monitoring measurements, when corrected for sampling bias. DAS is not aware of the existence of a written statement in OPP FQPA science policy documents specifying that model accuracy within an order of magnitude is the degree of accuracy needed for human health risk assessment. EPA guidance requires this statement as a step in defining regulatory objectives (USEPA, 2009). This requirement was discussed in detail in previous comments (Oliver et al. 2015), but no definition of the regulatory objective has been supplied.

Because of all of these issues with the Agency's evaluation, its conclusions that the PWC modeled estimates are "reasonable" reflections of real-world conditions is further weakened and

again indicates that additional efforts are required to produce a scientifically defensible assessment.

D. EPA Has Not Responded to any Registrant Comments to Previous Assessments, Nor Has the Agency Considered or Referenced any Additional Submissions or Proposals from the Registrant.

EPA's efforts in the assessment of the potential for presence of chlorpyrifos in surface water resources spans a number of years, extending to the interim reregistration eligibility decision in 2001. In the current round of EPA Registration Review, the first drinking water assessment was released in 2011 (Bohaty, 2011). DAS, as the primary registrant, along with other members of the public, submitted detailed technical comments to the docket. In response to these comments, the Agency produced an updated drinking water assessment in 2014 (Bohaty, 2014). However, there were many technical areas that were not addressed in EPA's 2014 assessment. These deficiencies were again noted in comments that DAS submitted in April 2015, in response to the 2014 updated assessment (Oliver et al. 2015). There has been no response from EPA to these comments.

On September 10, 2015, EPA met with DAS to discuss possible refinement elements available for drinking water assessments (USEPA, 2015). DAS presented a proposal for data-driven refinement, which was not inconsistent with what EPA had presented in its December 2014 Revised Human Health Risk Assessment. In the summary of the meeting, EPA stated that "EPA will evaluate whether the proposal presented by DAS is appropriate to support refinements to risk assessments." September 2015 EPA Meeting at 1 (cover page). Such an evaluation was never received by DAS, nor was the meeting cited in the current assessment.

Since no feedback was received on the concepts proposed in the September 10, 2015 meeting, DAS undertook an effort to set forth these concepts in a refined national-scale assessment (Perkins et al. 2016; MRID 50016001), which DAS submitted to the Agency in February, 2016. EPA has not given any indication that they have undertaken any technical review of MRID 50016001, and EPA has made no formal or informal mention of the study, in the current assessment or elsewhere.

In the meantime, EPA was preparing the current drinking water assessment, whose transmission memorandum is dated April 14, 2016. However, the document was not released to the federal docket until late November, 2016. It is unfortunate that the Agency chose to withhold

the assessment for seven months when significant scientific progress could have been made to more realistically reflect the actual use of the product. The Agency has indicated that there are avenues for refinement of the assessment (for example, by the application of Percent Cropped Area (PCA) factors or reflecting label changes). However, it does not appear that EPA has any intention of engaging in refinement discussions, as the current assessment states: "This highly refined drinking water assessment updates and completes the Agency's examination of exposure through drinking water for all registered uses of chlorpyrifos" Drinking Water Assessment at 12.

As the current assessment stands, it is insufficient for final regulatory decision-making and can only be viewed as a preliminary, screening-level step. In order to evaluate exposure for input into aggregate human health assessment, continued EPA work is required at the very least to refine the assessment using the data already available to the Agency and to allow the assessment to move beyond its current realm of speculation and unsupported conclusions. Ultimately, a wholesale rethinking of the exposure assessment paradigm is sorely needed through the development of an appropriate assessment framework that more realistically represents the agricultural landscape and drinking water resources. This would allow the Agency to execute useful drinking water exposure assessments that would result in defensible science-driven regulatory decisions.

E. EPA's Drinking Water Assessment Warrants SAP Review.

EPA's refined drinking water assessment for chlorpyrifos is based upon the Agency's standard IR formulation, which has been in use as a screening-level tool since the late 1980s, and which has not been reviewed by a SAP since 1988. Thus, EPA's assessment does not consider many options for refinement that have been proposed specifically for chlorpyrifos by DAS and several experts during previous comment periods and in DAS's study submitted to EPA in early 2016. Refinements have also been proposed through scientific conferences, Environmental Modeling Public Meeting presentations and through CLA. EPA's failure to consider these approaches to refinement warrants independent review. EPA should bring these refinement techniques to a SAP and seek guidance on how to make their assessments reflect the best available science before using an approach that was last reviewed eighteen years ago.

EPA attempts to make the current assessment appear probabilistic in nature by simulating different crops; however, the results are all considered to be equally probable and are all cases

that "could happen" by assuming that an entire drinking water source watershed contains the crop (100% Percent Cropped Area ("PCA") and that the entire area is treated on a single day at worst-case application rates and timings. Indeed, within the IR methodology, a PCA of <100% is recommended as a refinement and EPA has published guidance on developing PCAs for major crops and some common combinations of two crops.[12] However, for a product such as chlorpyrifos, with many crop uses potentially occurring in the same watershed but with different cropping management practices and application rates and timing, the PCA methodology in the EPA's 2014 guidance is insufficient; it is necessary to bring more detailed and available cropping intensity data into the analysis to truly refine the assessment. This point was noted in the 2014 PCA guidance, which recommended the use of the USDA National Agricultural Statistics Service Cropland Data Layer ("CDL") as a data source. Such an approach was submitted to EPA by DAS in February 2016 following discussions with the Agency in a meeting with EFED in September 2015 (September 2015 EPA Meeting, EPA-HQ-OPP-2008-0850-0853). The DAS submission offered a pragmatic and still conservative consideration of PCA that resulted in a significant refinement of modeled drinking water estimates.

In addition, EPA performed some preliminary analysis of a nationwide (but not publicly-available) database of validated drinking water watersheds and intakes that could aid in identifying drinking water sources at potential risk from pesticides. However, the Agency did not apply any results of the analysis in the current assessment, because of perceived incompleteness or uncertainties in that database. The potential degree of over-estimation of exposures due to this lack of refinement and recommendations on appropriate use of best methodologies and available approaches further warrant independent SAP review.

References:

Bohaty RFH, Revised Chlorpyrifos Preliminary Registration Review Drinking Water Assessment, EPA-HQ-OPP-2008-0850-0026 (June 20, 2011)

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[12] EPA, *Development of Community Water System Drinking Water Intake Percent Cropped Area Adjustment Factors for use in Drinking Water Exposure Assessments: 2014 Update,* https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/development-community-water-system-drinking-water.

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EPA, Guidance on the Development, Evaluation, and Application of Environmental Models (Mar. 2009).

EPA, Development of Community Water System Drinking Water Intake Percent Cropped Area Adjustment Factors for use in Drinking Water Exposure Assessments: 2014 Update. Environmental Fate and Effects Division, Office of Chemical Safety and Pollution Prevention.

9-September-2104, https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/development-community-water-system-drinking-water (accessed Jan. 5, 2017).

EPA, Meeting between Dow AgroSciences (DAS) and EPA where DAS presented eight actionable concepts for refining predictions of surface water concentrations, EPA-HQ-OPP-2008-0850-0853 (Sept. 2015).

EPA, Biological Evaluation Chapters for Chlorpyrifos ESA Assessment; Attachment 1-3, "Method for Established the Use Site Footprint" https://www3.epa.gov/pesticides/nas/attachment-1-3.docx, (accessed Jan. 3, 2017).

XII. EPA's Proposed Revocation of Tolerances Should be Considered a Significant Regulatory Action.

EPA assessments underestimate the economic impact of revocation of chlorpyrifos tolerances. U.S. growers and farmers have expressed the critical need for and value of chlorpyrifos in previous and current comments, which EPA has not recognized in its current assessments. EPA's proposed revocation of tolerances will impact U.S. growers, many of them small family farms, along with food processors and distribution companies. It will also negatively affect global trade of key consumer-important crops and crop products into the United States. When combined, the economic impact could easily make the proposed revocation of tolerances a significant regulatory action.

A. EPA's Proposed Revocation of Tolerances Does Not Accurately Consider the Economic Impact to U.S. Agriculture.

EPA's NODA and accompanying assessments do not include an update or full evaluation of the important production and economic impacts of the proposed tolerance revocations. The only economic evaluation appears to be the EPA Analysis of the Small Business Impact of Revoking Chlorpyrifos Food Tolerance from 2015 (USEPA, 2015). This analysis was challenged in comments by DAS previously submitted to the docket in 2016 (Oliver et al. 2016). In addition, a study of the benefits of chlorpyrifos to U.S. growers was also submitted to the docket in 2016 (Nelson and Schneider, 2016b). Neither has been responded to by EPA or considered in the NODA.

U.S. agriculture recognizes the impact of the proposed revocation of tolerances, which would effectively cause the loss of their uses of chlorpyrifos. Twenty-three hundred (2,300) U.S. growers, many of them representing family farms, have expressed their need for chlorpyrifos on the critical crops of corn, soybean, wheat, cotton, alfalfa, and sugar beets, along with multiple

other crops through petitions submitted to the current docket. EPA-HQ-OPP-2015-0653. In addition, multiple grower groups have provided comments expressing the need for chlorpyrifos in previous and the current comment periods. Oliver et al. (2016) identified several failings of the EPA's analysis of Small Business Impact which cause a significant underestimation of the potential impact:

- The focus only on control of primary pests fails to fully account for all reasons a grower needs chlorpyrifos. These other documented reasons should be considered rather than being dismissed as "uncertainties" and then not evaluated as in the current assessment.

- The impact in particular regions can be expected to be more severe than shown in EPA's national-level assessment. EPA's conclusion that even in these regions "relatively few additional farms may be impacted" is unsupported by the evidence presented. Region-specific assessments are needed.

Chlorpyrifos contributes significantly to the control of insect pests in a wide range of corps including cereal, oil, forage, fruit, nut, and vegetable crops. In some situations, it is the only tool growers have for controlling a serious pest and maintaining their profitability. A more complete analysis of the value of chlorpyrifos shows there are many reasons growers rely on chlorpyrifos (Nelson and Schneider, 2016b):

- Reliable control of a broad spectrum of insect pests;

- Active on foliar-feeding and soil-dwelling insect pests;

- Fast knockdown;

- Significantly less disruptive to beneficial populations than some other insecticides and does not flare mites or aphids;

- Flexible application timing and method;

- Important tank mix partner for controlling tough pests;

- Good rotational partner to manage insect resistance;

- Easily implemented into existing IPM and IRM programs;

- Excellent safety on the crop;

- Broad label;

- International tolerances and maximum residue limits in place in export destination countries;
- Moderate mammalian toxicity;
- Easy to handle; and
- Strong technical support database

Each of the attributes listed above carries an economic value for the individual grower, and therefore each also carries an economic impact if tolerances for chlorpyrifos are revoked.

B. Revocation of Tolerances Will Have Significant Negative Impacts on Trade.

Today, chlorpyrifos is registered in about 100 countries for use on more than fifty different crops against damage caused by a wide-range of insect pests. Revoking chlorpyrifos tolerances would result in significant disruption in the pest management practices used in the production of certain import crops, disruption of long-standing trade relationships, and create a new set of winners and losers as market participants adapt to regulatory changes. This represents a significant impact on trade with particular relevance to developing countries that rely on exports of agricultural commodities to the United States (Nelson and Schneider, 2016a).

In an assessment focused on chlorpyrifos use on key crops exported to the United States from several important trading partners, including Brazil, Canada, Costa Rica, Israel, Mexico, Morocco, South Africa, and Spain, Nelson and Schneider (2016) reported potentially significant economic impact from both the perspective of consumers and food chain members in the United States and also from the perspective of the exporting countries:

- Citrus fruit and essential oils of citrus (Mexico), wine (Italy), and soybeans (Brazil) are the U.S. imports most impacted by revoking chlorpyrifos' tolerances because of the large proportion of each commodity imported from these countries and the large crop area treated with chlorpyrifos.
- From the export partners' perspective, citrus fruit and essential oils of citrus (Mexico), wine (Italy), soybeans (Brazil), essential oils of citrus (Israel, South Africa, Spain), sorghum (Mexico), and sugar (Costa Rica) are the exports most impacted by revoking chlorpyrifos' tolerances because of the large proportion of each commodity exported from these countries to the U.S. and the large crop area treated with chlorpyrifos.

References

Nelson, J.E., Schneider, L.L. 2016a. The Impact of Revoking Chlorpyrifos Tolerances (MRLs) on U.S. Agricultural Imports from Key Food Exporting Countries. Nelson-Schneider Consulting LLC. Submitted to docket: EPA-HQ-OPP-2015-0653, January 2017.

Nelson, J.E., Schneider, L.L. 2016b. Use and Benefits of Chlorpyrifos in Agriculture. Nelson-Schneider Consulting LLC. Submitted to docket EPA-HQ-2015-0653, January 2016.

Oliver, G., Poletika, N., Burns, C., Juberg, D., Hastings, K., Velovitch, J., Richardson, J., Racke, K., Bartels, M., Marty, S. 2016. Dow AgroSciences Response to EPA's: Chlorpyrifos; Tolerance Revocations; Proposed Rule and EPA Analysis of the Small Business Impacts of Revoking Chlorpyrifos Food Tolerances at 126. EPA-HQ-OPP-2015-0653-0386.

EPA, Analysis of the Small Business Impact of Revoking Chlorpyrifos Food Tolerances, EPA-HQ-OPP-2015-0653-002 (Oct. 27, 2015).

XIII. Principles of Sound Science and Good Government Warrant that EPA Must Deny the Petition and Convene the SAP to Review the RHHRA and 2016 Drinking Water Assessment for Chlorpyrifos.

EPA appears to be exploiting a court-imposed deadline while sacrificing science, objectivity, and the Agency's own credibility to achieve its desired regulatory policy goals. EPA should immediately deny the Petition and convene the SAP to review the RHHRA and 2016 drinking water assessment for chlorpyrifos. After taking guidance from the SAP on these important issues, the Agency must complete Registration Review pursuant to FIFRA and address the issues raised herein and in the additional comments to the chlorpyrifos docket raised by DAS and other stakeholders before taking final action with respect to chlorpyrifos. Registration Review will allow the Agency to complete its assessment of chlorpyrifos in a thorough, science-based manner in keeping with the Agency's statutory mandates. Completing Registration Review would go a long way toward restoring the transparency in the regulatory process for chlorpyrifos that has been sorely lacking since EPA's abrupt shift in policy in 2015.

Appendix A

Prior DAS Comments and Other Submissions to EPA that Should be Considered by the Agency

1. Edwards, D., Juberg, D., Burns, C., Goodman, J., Li, A., Bartels, M., Lickfeldt, D. (2013). Epidemiology Studies Pertaining to Chlorpyrifos Exposures: Consideration of Reliability and Utility. Submitted by Dow AgroSciences to EPA November 12, 2013. (EPA-HQ-OPP-2008-0850-0511; EPA-HQ-OPP-2015-0653-0201).

2. Poet, T.S. (2015). Multi-Route, Lifestage, and Pregnancy PBPK/PD model for Chlorpyrifos and Chlorpyrifos-Oxon: Model development and validation. A report of the Summit Toxicology Group, dated April 2015. (EPA-HQ-OPP-2008-0850-0514).

3. Reiss, R. (2015). Review of EPA's Occupational and Residential Exposure Assessment for Chlorpyrifos. Exponent. Project Identification 1500180.000, dated April 2015 (submitted to docket: EPA-HQ-2008-0850).

4. Gradient's Comments on the EPA's Revised Human Health Risk Assessment of Chlorpyrifos, dated April 24, 2015. (EPA-HQ-OPP-2008-0850-0508).

5. Mosquin, P.L., Aldworth, J. (2015), A Review of the Updated Chlorpyrifos Drinking Water Assessment. Technical Report of RTI International, dated April 28, 2015. (EPA-HQ-OPP-2008-0850-0551; EPA-HQ-OPP-2015-0653-0053).

6. Oliver, G., Juberg, D., Burns, C., Bartels, M., Velovitch, J., Poletika, N., Khoshab, A., Racke, K., Martin, D., Felming, C., Richardson, J. (2015). Dow AgroSciences LLC's Response to EPA's Revised Human Health Risk Assessment for Chlorpyrifos Registration Review, dated April 29, 2015. (EPA-HQ-OPP-2008-0850-0845; EPA-HQ-OPP-2015-0653-0214).

7. Oliver, G., Juberg, D., Burns, C., Bartels, M., Marty, S., Velovitch, J. Khoshab, A., Hastings, K., Racke, K., Dow AgroSciences LLC's Response to EPA's Chlorpyrifos-Methyl: Human Health *Draft* Risk Assessment ("DRA") for Registration Review, dated November 18, 2015. (EPA-HQ-OPP-2010-0119-0044).

8. Burns, C. (2015). Comments on EPA's Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides, dated December 22, 2015 (EPA-HQ-OPP-2010-0119-0045; EPA-HQ-OPP-2015-0653-0230).

9. Reiss, R. (2015). A Review of EPA's Drinking Water Exposure Assessment for Chlorpyrifos, dated April 28, 2015. (EPA-HQ-OPP-2008-0850-0792; resubmitted to docket: EPA-HQ-OPP-2015-0653).

10. Marty, M. S., Marshall, V. A. (2014). Characterization of Cholinesterase (ChE) Inhibition Following Acute Exposure to Chlorpyrifos-Oxon ("CPFO") in Drinking Water. A report of The Dow Chemical Company (submitted to EPA in 2015).

11. Nelson, J.E., Schneider, L.L. (2016b). Use and Benefits of Chlorpyrifos in Agriculture. Nelson-Schneider Consulting LLC, dated January 4, 2016. (EPA-HQ-OPP-2015-0653-0227).

12. Oliver, G., Poletika, N., Burns, C., Juberg, D., Hastings, K., Velovitch, J., Richardson, J., Racke, K., Bartels, M., Marty, S. (2016). Dow AgroSciences Response to EPA's: Chlorpyrifos; Tolerance Revocations; Proposed Rule and EPA Analysis of the Small Business Impacts of Revoking Chlorpyrifos Food Tolerances, dated January 4, 2016. (EPA-HQ-OPP-2015-0653-0386).

13. Oliver, G., Dow AgroSciences Legal and Policy Comments in Response to EPA's Proposed Rule to Revoke Tolerances for Chlorpyrifos, dated January 5, 2016. (EPA-HQ-OPP-2015-0653-0266).

14. Oliver, G., Dow AgroSciences LLC's Legal and Policy Comments in Response to (i) EPA's Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides and (ii) EPA's Chlorpyrifos-Methyl: Human Health Draft Risk Assessment for Registration Review, dated February 19, 2016. (EPA-HQ-OPP-2010-0119-0033).

15. Perkins, D.B.; Jones, K.; Amos, J.J.; Snyder, N.J.; Wright, K.N.; Guth, N. (2016) Chlorpyrifos: Preliminary National-scale Refined Drinking Water Exposure Assessment; Unpublished study of Dow AgroSciences, performed by Waterborne Environmental, Inc. DAS study ID 151193, 19-Feb-2016. MRID 50016001.

16. Dow AgroSciences LLC's Request for EPA to (i) Explain its Reliance on Epidemiology Studies in the Face of Incomplete and Insufficient Underlying Raw Data and (ii) Reopen the Comment Periods for EPA's Revised Human Health Risk Assessment for Chlorpyrifos and Proposed Rule to Revoke all Chlorpyrifos Tolerances, dated March 30, 2016. (EPA-HQ-OPP-2016-0062-0107).

17. Dow AgroSciences LLC's Petition to Postpone the April 2016 FIFRA SAP, dated April 4, 2016. (EPA-HQ-OPP-2016-0062-0106).

18. Initial Comments by Dow AgroSciences LLC to the Scientific Advisory Panel, dated April 8, 2016. (EPA-HQ-OPP-2016-0062-0110).

19. Dow AgroSciences Additional Comments for the EPA's FIFRA Scientific Advisory Panel ("SAP"): Chlorpyrifos: Analysis of Biomonitoring Data (April 19-21), dated April 15, 2016. (EPA-HQ-OPP-2016-0062-0123).

20. Driver, J., Ross, J., Comments to Chlorpyrifos Issue Paper: Evaluation of Biomonitoring Data from Epidemiology Studies, dated April 16, 2016. (submitted to docket: EPA-HQ-OPP-2016-0062).

21. Nelson, J.E., Schneider, L.L. (2016a), The Impact of Revoking Chlorpyrifos Tolerances (MRLs) on U.S. Agricultural Imports from Key Food Exporting Countries. Nelson-Schneider Consulting LLC, dated January 2017. (submitted to docket: EPA-HQ-OPP-2015-0653).

January 17, 2017

OPP Docket
Environmental Protection Agency
Docket Center (EPA/DC), (28221T)
1200 Pennsylvania Ave. NW.
Washington, DC 20460-0001

Appended below are the names of 32,176 individuals who have submitted public comments urging the Environmental Protection Agency to ban all uses of the neurotoxic pesticide chlorpyrifos. In addition to signing on in support of the following letter, 2,889 individuals of the total number have submitted personalized comments. The personalized comments start on page 2 and end on page 231.

Ban chlorpyrifos now (RE: EPA-HQ-OPP-2015-0653-0402)

Dear Environmental Protection Agency:

I urge the U.S. Environmental Protection Agency to ban all uses of the neurotoxic pesticide chlorpyrifos immediately. Whenever this chemical is sprayed in the air, it can cause both immediate and long-term health harms to farmworkers, kids and others who are exposed. Every year, chlorpyrifos spraying in agricultural fields poisons farmworkers and other people exposed to pesticide drift in the air. This chemical is also linked to reduced IQ and attention deficit disorders in children. Just last year the EPA released an updated assessment of chlorpyrifos and concluded that current safety standards are not enough to protect public health.

The EPA should take immediate steps to ban this brain-damaging pesticide to:

- Protect children from learning and memory impairments
- Protect communities from poisoning when the pesticides drift off crops and into nearby neighborhoods and schools
- Prevent contamination of our food
- Prevent contamination of our drinking water
- Prevent worker poisonings and harm to their children

Action on this toxic chemical is long overdue. I urge you to ensure that your agency moves quickly to ban chlorpyrifos now.

Thank you for your consideration of this important issue.

Sincerely,

The Undersigned

Gertrude Armstrong
Hopewell, NJ 08525-2043
"We need to do a better job of protecting our children. My daughter was born with a birth defect linked to pesticides. Let's go. We can do better than this. Our children are our top priority, not chemical company's profits. Thank you for reading my letter."

Grace Diaz
Albany, NY 12208-2612
"I lived in the Lower Yakima Valley of Washington State for 7 years. I experienced the effect of pesticides first hand. We cannot continue to harm hard-working farmers and farmhands, as well as children and others living in the farming areas."

Angela Garcia-johnson
West Chester, OH 45069-4367
"The EPA was set up to protect the citizens of our country. This agency would best serve the populous by banning chlorpyrifos and similar poisons from the marketplace. Act now, before more harm is done to the Earth and it's inhabitants. Enough is enough."

Joyce Greenberg
Highmount, NY 12441-0238
"All life on the planet is bombarded daily by toxic chemicals, pesticides--all kinds of poisons. Mostly the poisons are to increase profits for corporations. But who pays the health care bills? Not the corporations."

Dorothy Johnson
Centreville, VA 20121-3036
"As an experienced Registered Nurse and lifelong health advocate, I am appalled that this highly neurotoxic pesticide is still being used!"

Debra Arend
Elk Grove Village, IL 60007-2803
"This affects all of us. You, your family, no one is immune to its toxicity. How can you think using chemicals is a good thing? There are consequences. We look to you to be our voice and to speak for the environment. To protect it, and us. Thank you"

Shawn Hughes
Denver, CO 80210-6006
"We need the EPA to protect our children's health over lobbyists and corporate greed of big agriculture. Please listen to the scientists and ban all pesticides that have been shown to be harmful/toxic to our health, bees and our environment."

Kate Burroughs
Sebastopol, CA 95472-2446
"Tell the EPA to do its job and ban toxic chemicals-ALL OF THEM! I am a certified organic farmer and know that farming CAN be done without toxic chemicals."

Esther Faber
Bellingham, WA 98225-2316
"We can not, in good conscience, allow chlorpyrifos to poison our water, air, food and our farm workers and their children. Do the right thing and ban this poison."

H. Fitzgerald
Sherman Oaks, CA 91413-0576
"Our precious environment is already overloaded with chemicals, the synergistic effect of which strikes me as requiring us all to play Russian roulette with our health and with the health of generations to follow. Thank you for reading my letter."

January 17, 2017

The Honorable Jim Jones
Assistant Administrator, Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W. Mail Stop 7101M
Washington, DC 20460

RE: Federal Register Notice; Chlorpyrifos; Tolerance Revocations; Notice of Data Availability and Request for Comment (Docket ID: EPA-HQ-OPP-2015-0653-0402)

Dear Mr Jones,

As the voice of more than 300 leading food, beverage and consumer product companies, the Grocery Manufacturers Association (GMA)[1] appreciates the opportunity to submit comments to the Environmental Protection Agency's (EPA's) proposed tolerance revocation of chlorpyrifos (Docket ID: EPA-HQ-OPP-2015-0653-0402).

In these comments GMA highlights two major concerns we have with the approach taken by the EPA in proposing the tolerance revocation of chlorpyrifos. First, the proposed action by EPA is based on the findings from a single epidemiology study (Columbia Study), which has been criticized by EPA's own Scientific Advisory Panel (SAP), and second, the proposed action bypasses the statutory procedures established under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to cancel a product registration.

[1] The Grocery Manufacturers Association (GMA) is the trade organization representing the world's leading food, beverage and consumer products companies and associated partners. The U.S. food, beverage and consumer packaged goods industry has facilities in 30,000 communities, generates $1 trillion in sales annually, contributes $415 billion in added value to the economy every year and is the single largest U.S. manufacturing industry with 1.7 million manufacturing workers. Founded in 1908, GMA has a primary focus on product safety, science-based public policies and industry initiatives that seek to empower people with the tools and information they need to make informed choices and lead healthier lives. For more information, visit gmaonline.org

Regarding our first concern, the scientific basis used by the EPA to propose the revocation of tolerance level has been questioned by the 2016 EPA SAP. The SAP report challenged the scientific validity of the Columbia Study. It therefore appears that the EPA selectively interpreted the Panel's report in a manner that justifies a precedent-setting departure from the process of evaluating potential risk and regulation of pesticides. Furthermore, EPA's use of the Columbia Study without reviewing the raw data is a major procedural change that allows the use of questionable assumptions as the basis of the agency's decisions.

Regarding our second concern, the EPA should follow its normal registration review process for the evaluation of chlorpyrifos. EPA's registration review procedures are well-established, comprehensive and transparent science-based processes that were specifically established under FIFRA. Until recently, the registration review process for chlorpyrifos has been proceeding under the FIFRA-compliant procedures. Recently, the Agency has pulled its evaluation of chlorpyriphos out of the normal registration review process and has proposed a decision without a full and thorough assessment. Under this unprecedented process, EPA would eliminate use of chlorpyriphos without adherence to the statutory procedures required by FIFRA.

The sudden loss of this widely-used crop protection agent outside of proper procedure will cause major disruptions in the supply of various ready to eat food and fresh produce. The impact will include product recalls and global trade implications.

GMA therefore requests that EPA follow established, transparent, science-based FIFRA registration processes in its evaluation of chlorpyriphos. We are confident that a procedurally and scientifically sound evaluation will provide strong support for the re-registration of chlorpyrifos. If EPA concludes that the tolerance of chlorpyrifos should be revoked based on the Columbia Study, the agency will set a scientifically and procedurally unsound precedent based on a single epidemiology study without the due process safeguards provided under FIFRA.

Sincerely,

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Earthjustice
Farmworker Association of Florida
Farmworker Justice
GreenLatinos
Labor Council for Latin American Advancement
League of United Latin American Citizens
Migrant Clinicians Network
National Hispanic Medical Association
Natural Resources Defense Council
Pesticide Action Network
Pineros y Campesinos Unidos del Noroeste
United Farm Workers

Comments on EPA Proposal To Revoke Chlorpyrifos Tolerances (EPA-HQ-OPP-2015-0653)
Submitted on January 17, 2017

INTRODUCTION

The Environmental Protection Agency ("EPA") released an update to its assessment of the human health risks posed by chlorpyrifos that confirms all uses of chlorpyrifos are unsafe and must be banned. These comments are submitted on behalf of Earthjustice, United Farm Workers, Natural Resources Defense Council, Pesticide Action Network, Farmworker Justice, California Rural Legal Assistance Foundation, National Hispanic Medical Association, Pineros y Campesinos Unidos del Noroeste, GreenLatinos, Migrant Clinicians Network, League of United Latin American Citizens, Labor Council for Latin American Advancement, and Farmworker Association of Florida.

EPA had previously found, based on studies from Columbia University and other academic institutions, that prenatal exposures to chlorpyrifos are correlated with lower IQ, loss of working memory, attention deficit disorders, and developmental delays. EPA, the academic researchers, and EPA's Scientific Advisory Panel ("SAP") all found that these brain damage impacts occur at far lower exposures than those associated with acute poisoning. Nonetheless, in its December 2014 chlorpyrifos revised human health risk assessment, EPA continued to use 10% cholinesterase inhibition as its regulatory endpoint. Our previous comments, as well as comments submitted by scientists and health professionals, explained why that endpoint was not protective and left people, and children in particular, vulnerable to extremely unsafe chlorpyrifos exposures.

EPA has now changed its regulatory endpoint. It has lowered what it deems to be allowable exposures to chlorpyrifos in an attempt to prevent brain damage from *in utero* exposures. Using this updated endpoint, EPA found the following alarming risks:

- All food exposures exceed safe levels, with the most exposed population being children between 1-2 years of age. This vulnerable age group is on average exposed to 140 times what EPA deems safe.
- There is no safe level of chlorpyrifos in drinking water.
- Drift of pesticides from the fields expose children to unsafe levels of chlorpyrifos within 300 or more feet of the fields where the pesticide is sprayed. Children could be exposed to toxic drift at schools and day cares, in their homes, or at playgrounds.

- All workers who mix and apply chlorpyrifos pesticides are exposed to levels greater than what EPA considers safe. That is the case even with the maximum possible protective clothing, equipment, and engineering controls.

- Field workers are currently allowed to re-enter fields within 1-5 days after pesticide spraying, but unsafe exposures continue on average for 18 days after applications.

Chlorpyrifos is contaminating our food and water and exposing workers and their families to poisonings, learning disabilities, and other needless harm.

EPA has proposed to revoke all food tolerances for chlorpyrifos and has found that all uses, including non-food uses, lead to drinking water contamination and dangerous exposures for workers and children. Since EPA proposed revoking chlorpyrifos tolerances, the European Union agreed upon new endpoints following an updated toxicological review of chlorpyrifos. Based on these new endpoints, the United Kingdom banned all but one use of chlorpyrifos on an expedited timeline. EPA should act with similar haste to ban all chlorpyrifos uses with an effective date not more than six months from the date of the revocation determination.

In addition to the sources cited within, these comments rely upon and incorporate the following attached documents: Petition for Emergency and Ordinary Suspension of Chlorpyrifos Uses that Pose Unacceptable Risks to Workers and Petition to Cancel All Uses of Chlorpyrifos, September 21, 2016 (Attachment 1); and Declaration of Philip J. Landrigan, M.D., M.Sc. in Support of Petition to Suspend and Cancel Chlorpyrifos Uses (Attachment 2).

I. EPA HAS APPROPRIATELY ESTABLISHED A REGULATORY ENDPOINT DESIGNED TO GUARD AGAINST BRAIN DAMAGE FROM PRENATAL EXPOSURES

EPA's use of a regulatory endpoint based on neurodevelopmental effects in the 2016 Chlorpyrifos Revised Human Health Risk Assessment ("RHHRA") comports with best science and ensures reasonable certainty of no harm as required by the Food Quality Protection Act ("FQPA"). *See infra*, section II. Historically, EPA has used 10% cholinesterase inhibition as the endpoint for chlorpyrifos and other organophosphate pesticides. However, in reconstructing the chlorpyrifos doses experienced by pregnant women that were associated with serious adverse neurodevelopmental impacts in their children, EPA found that the pregnant mothers would have had less than 1% cholinesterase inhibition. RHHRA at 13. In other words, EPA determined that the neurodevelopmental harm occurred when the mothers were exposed to far lower doses of chlorpyrifos than what produces 10% cholinesterase inhibition. EPA considered both epidemiological studies and toxicological studies conducted on animals in making its determination. Based on these findings and the FQPA safety standard, EPA needed to either update its regulatory end point or add safety factors to account for these risks. EPA's approach is appropriate, scientifically defensible, and serves to adequately protect pregnant women and children.

A. EPA and Multiple SAPs, Including the 2016 SAP, Recognized That Using 10% Cholinesterase Inhibition Does Not Protect Kids

EPA, the 2012 SAP and the 2016 SAP all agree that the point of departure used in the 2014 chlorpyrifos human health risk assessment based on 10% cholinesterase inhibition does not account for neurodevelopmental effects and, therefore, is not sufficiently protective:

> In summary, these lines of evidence suggest that chlorpyrifos can affect neurodevelopment at levels lower than those associated with AChE inhibition, and that the use of AChE inhibition data may not be the most appropriate for dose-response modeling and derivation of a point of departure for assessment of the neurodevelopmental risks of chlorpyrifos.[1]

> The agency agrees with the 2016 FIFRA SAP (and previous SAPs) that there is a potential for neurodevelopmental effects associated with chlorpyrifos exposure to occur at levels below 10% RBC AChE inhibition, and that EPA's existing point of departure (which is based on 10% AChE inhibition) is therefore not sufficiently health protective. 81 Fed. Reg. 81,049, 81,050 (Nov. 17, 2016).

> The Panel agrees that both epidemiology and toxicology studies suggest there is evidence for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% red blood cell (RBC) acetylcholinesterase (AChE) inhibition (i.e., toxicity at lower doses).[2]

B. EPA's Revised Approach is Consistent with the Science on Neurodevelopmental Impacts and Its Proposal to Cancel All Food Tolerances will Protect Kids

In order to address the neurodevelopmental effects and protect kids, EPA needed to change its approach to the point of departure, which is exactly what the agency has done in the 2016 assessment:

> The 2014 revised human health risk assessment used dose-response data on acetylcholinesterase inhibition (AChI) [sic] in laboratory animals to derive a point of departure. However, the EPA believes that evidence from epidemiology studies indicates effects may occur at lower exposures than indicated by the toxicology database. The 2016 revised human health risk assessment uses neurodevelopmental effects as the critical effect, taking into account

[1] FIFRA SAP Meeting Minutes No. 2012-04: A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding Chlorpyrifos Health Effects (Apr. 2012) at 53, *available at* https://www.epa.gov/sites/production/files/2015-06/documents/041012minutes.pdf.

[2] FIFRA Scientific Advisory Panel Minutes No. 2016-01: A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding Chlorpyrifos: Analysis of Biomonitoring Data (Apr. 2016) at 18, *available at* https://www.epa.gov/sites/production/files/2016-07/documents/chlorpyrifos_sap_april_2016_final_minutes.pdf.

recommendations from the 2016 chlorpyrifos SAP on deriving a point of departure for risk assessment.[3]

EPA appropriately retained the FQPA safety factor. The agency chose a total value of 10X, but as discussed at greater length in our 2015 comments, the total FQPA safety factor should be greater than 10X due to uncertainties and concerns about prenatal toxicity.[4]

Briefly, EPA has previously set FQPA safety factors at greater than 10X to account for incomplete data and prenatal toxicity. Table 1 provides examples from past assessments that set FQPA safety factors greater than 10X when there are both data deficiencies and concerns for prenatal toxicity. Through these assessments, EPA has established a practice of setting the FQPA safety factor at more than 10X when appropriate based on its consideration of both data completeness and special FQPA concerns.

Table 1. **Uncertainty and safety factors used by EPA in past pesticide assessments**.

Pesticide	**Intra-species Factor**	**Inter-species Factor**	**Data Completeness Factor** *(specific data deficiency)*	**Special FQPA concerns** *(factors contributing to degree of concern)*
Carbendazim (MBC)[5]	10X	10X	3X (extrapolation from LOAEL)	10X (increased prenatal susceptibility in rat and rabbit studies)
Molinate[6]	10X	10X	3X (extrapolation from LOAEL)	10X (prenatal toxicity in rodent studies; uncertainties in drinking water exposure)
Pirimiphos-methyl[7]	10X	10X	10X (extrapolation from LOAEL, severity of effects at LOAEL, data gaps for long term studies)	3X (lack of complete toxicity database for assessing potential for susceptibility)

One of the most common situations in which EPA has established a higher safety factor is when the animal studies lack a no observable adverse effect level ("NOAEL") and the agency selects a lowest observed adverse effect level ("LOAEL") as the point of departure. In the 2016 assessment, EPA wrote, "The [time weighted average] blood level resulting from chlorpyrifos exposure from the crack and crevice scenario is considered a [LOAEL], since this is the exposure

[3] EPA website, https://www.epa.gov/ingredients-used-pesticide-products/revised-human-health-risk-assessment-chlorpyrifos.

[4] Farmworker and Conservation Comments on Chlorpyrifos Revised Human Health Risk Assessment (Apr. 30, 2015) at 17-23, Docket No. EPA-HQ-OPP-2008-0850.

[5] EPA. Revised Preliminary Human Health Risk Assessment: Thiophanate-methyl. Health Effects Division, Office of Pesticide Programs at 8-9 (April 25, 2002).

[6] EPA OPP, Health Effects Division, Human Health Risk Assessment: Molinate at 6, 14 (November 6, 2002).

[7] EPA OPP, Health Effects Division, Interim Reregistration Decision for Pirimiphos-Methyl: Case No. (2535) at 7 (July 31, 2006).

level likely to be associated with neurodevelopmental effects reported in the [Columbia Center for Children's Environmental Health] study." RHHRA at 4. Accordingly, EPA should have considered whether the FQPA safety factor should be greater than 10X to account for the additional uncertainty when extrapolating from a LOAEL in addition to the increased vulnerability of infants and children.

These safety factor considerations apply regardless of the endpoint used to determine the point of departure, as we noted in our 2015 comments. The data deficiencies and prenatal toxicity concerns for chlorpyrifos warrant an FQPA factor greater than 10X whether EPA was using an endpoint of 10% cholinesterase inhibition (as in their 2014 assessment) or an endpoint of neurodevelopmental impacts, as in the current assessment.

C. Following the Advice of the 2016 SAP, EPA Used the PBPK Model and Standard Exposure Assessment Protocols to Derive the Time Weighted Average Blood Concentration of Chlorpyrifos

As noted by EPA, the 2016 SAP was supportive of using the physiologically based pharmacokinetic ("PBPK") model as a tool to analyze exposure data: "Multiple Panel members noted that PBPK modeling is a valuable tool to interpret the biomonitoring data in circumstances where multiple routes of exposure occur and when based on best available information as inputs." 2016 SAP at 18. Further, the 2016 SAP recommended using the PBPK model to predict a time weighted average blood concentration predicted for women in the Columbia Center for Children's Environmental Health ("CCCEH") cohort: "…the estimated peak blood concentration or time weighted average (TWA) blood concentration within the prenatal period should be designated as the point of departure (PoD) for risk assessment…" *Id*. at 42.

EPA determined that the CCCEH cohort women most likely experienced exposure from crack-and-crevice application of chlorpyrifos based on information from professional pest control applicators, and the fact that other common residential uses were phased out in 1997. RHHRA at 14-15. EPA followed the SAP's advice and estimated exposures from the crack-and crevice chlorpyrifos application using standard, peer-reviewed methods and inputs, including the following:

- 2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment (Residential SOPs);
- Amount of chlorpyrifos residue that dissipates daily: based on all available chlorpyrifos-specific floor residue data;
- Post-application exposure durations: from EPA Exposure Factors Handbook 2011; and
- Female bodyweight: from EPA Exposure Factors Handbook 2011.

RHHRA at 16-17. The predicted time weighted average blood concentration, 4 pg/ g (0.004 ug/ L), is reasonable in comparison to the measurements from the CCCEH study women, which

ranged from 0.8-19.3 pg/g in 1999. EPA 2016 Chlorpyrifos Issue Paper: Evaluation of Biomonitoring Data from Epidemiology Studies at 14.

Furthermore, EPA's application of the time weighted average blood concentration to young children is supported by data from animal studies showing that the post-natal period is a window of susceptibility.[8]

D. The 2016 Chlorpyrifos Assessment is an Appropriate and Scientifically Defensible Use of Epidemiologic and Biomonitoring Information

While both the 2014 and 2016 chlorpyrifos risk assessments use the PBPK model sponsored by Dow AgroSciences for deriving internal dosimetry measures,[9] the 2016 RHHRA has several important improvements over the earlier 2014 assessment. Whereas the 2014 assessment used 10% cholinesterase inhibition as a Point of Departure ("PoD"), in the 2016 assessment EPA followed the recommendations of its SAP to address the risks below 10% cholinesterase inhibition because, "epidemiology and toxicology studies suggest there is evidence for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% [cholinesterase inhibition]." RHHRA at 10 (quoting 2016 SAP). By using the CCCEH epidemiologic data to inform the PoD, the new 2016 risk assessment better addresses the elevated risks to vulnerable and sensitive populations from real-world exposures, including levels below those that trigger a 10% cholinesterase inhibition.

1. Epidemiologic data and biomonitoring from unintentional human exposures provide valuable information used across EPA programs to calculate risk estimates and support regulations.

To generate accurate and relevant risk assessments, EPA should use all available information relevant to hazard, exposure, use, manufacturing process, disposal, and other aspects of the life cycle of chemicals. In particular, occupational or environmental epidemiologic studies – cohort, case-control, ecological, and others – can provide very valuable information to inform risk evaluation because such studies capture real-world exposure conditions that do not exist in laboratory settings. As noted in EPA's Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment:

> Specifically, these types of human information provide insight into the effects caused by actual chemical exposures in humans and thus can contribute to problem formulation and hazard/risk characterization. In addition, epidemiologic and human incident data can guide additional analyses or data generations (*e.g.*, dose and endpoint selection for use in in vitro and targeted in vivo experimental

[8] Animal studies are reviewed in EPA's 2014 Revised Human Health Risk Assessment for Chlorpyrifos, pg. 25-26. Specifically, EPA finds that, "There is a considerable and growing body of literature on the effects of chlorpyrifos on the developing brain of laboratory animals (rats and mice) indicating that gestational and/or postnatal exposure may cause persistent behavioral effects into adulthood. These data provide support for the susceptibility of the developing mammalian brain to chlorpyrifos exposure."

[9] Comments submitted to EPA by Professors Whyatt, Slotkin and Hattis provide a detailed analysis of serious weaknesses in EPA's use of a model provided by Dow AgroSciences. Docket ID: EPA-HQ-OPP-2008-0850-0510, EPA-HQ-OPP-2008-0850-0100, EPA-HQ-OPP-2008-0850-0092, and EPA-HQ-OPP-2008-0850-0089.

studies), identify potentially susceptible populations, identify new health effects or confirm the existing toxicological observations.[10]

The EPA IRIS program has effectively and appropriately used epidemiologic and human biomonitoring data from unintentional exposure studies to calculate risk estimates and support regulatory decisions. For example:

- Mercury (IRIS 2012). Epidemiologic data (the Faroe Islands analysis) was used quantitatively in EPA's evaluation of risk for methylmercury, as recommended by the National Academies.[11] EPA based the oral RfD on lasting neurological effects in children exposed during early life (Grandjean et al., 1977; Budtz-Jorgensen et al., 1999).[12]

- Tetrachlorethylene (IRIS 2012). EPA IRIS risk assessment of tetrachloroethylene (perchloroethylene), which was reviewed and approved by the National Academies in 2010, used both epidemiologic and animal study data, along with a pharmacokinetic model,[13, 14] similar to the data-integration approach used by EPA in this 2016 chlorpyrifos assessment.

- 1,3-Butadiene (IRIS 2002). Generated the cancer risk from inhalation exposure based on the epidemiologic study of styrene-butadiene rubber production workers (Delzell et al., 1995). Health Canada used the same data and same approach for its cancer risk estimate.[15]

- Benzene (IRIS 2003). The oral RfD was based on decreased lymphocyte count in a workplace epidemiologic study (Rothman et al., 1996). The RfD is based on route-to-route extrapolation of the results of benchmark dose (BMD) modeling of the absolute lymphocyte count (ALC) data from the occupational epidemiologic study by Rothman et al. (1996), in which workers were exposed to benzene by inhalation. Rothman et al. (1996) conducted a cross-sectional study of 44 workers exposed to benzene and 44 age- and gender-matched unexposed controls.

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[10] EPA Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment (2010) at 7.

[11] NRC 2010. EPA's Methylmercury Guideline Is Scientifically Justifiable For Protecting Most Americans, But Some May Be at Risk. National Academy of Sciences Press release, July 11. http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=9899.

[12] https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0073_summary.pdf.

[13] EPA 2012. Toxicological review of Tetrachloroethylene. February. EPA/635/R-08/011F https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0106tr.pdf.

[14] NRC 2010. National Research Council. Review of the Environmental Protection Agency's Draft IRIS Assessment of Tetrachloroethylene. Washington, DC: The National Academies Press.

https://www.nap.edu/catalog/12863/review-of-the-environmental-protection-agencys-draft-iris-assessment-of-tetrachloroethylene.

[15] https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=139.

Twenty-one of the 44 subjects in the exposed and control groups were female. Mean (standard deviation) years of occupational exposure to benzene were 6.3 (4.4), with a range of 0.7-16 years. Benzene exposure was monitored by organic vapor passive dosimetry badges worn by each worker for a full workshift on 5 days within a 1-2 week period prior to collection of blood samples.[16]

- Arsenic carcinogenicity (IRIS 1991). EPA classified arsenic as a human carcinogen based on sufficient evidence of lung cancer deaths in multiple epidemiologic studies of inhalation exposures, and organ cancers (liver, kidney, lung, bladder) and skin cancers in populations consuming inorganic arsenic-contaminated drinking water. The animal data were considered inadequate. EPA calculated the cancer risk estimate based on the oral dose-response data from a study of a Taiwan population exposed through drinking water (Tseng et al., 1968; Tseng 1977). The inhalation cancer risk estimate was based on epidemiologic evidence of lung cancer in men exposed occupationally (Brown and Chu 1983, Lee-Feldstein 1983; Higgins 1982; Enterline and Marsh, 1982).[17]

IRIS risk assessments are used by states and local governments, federal agencies, and countries worldwide, to support regulatory decisions such as air quality and water quality standards to protect public health and to set cleanup standards for hazardous waste sites.

Epidemiological studies have a long history as the basis for regulatory decision-making and standard setting to reduce exposures to lead, another developmental neurotoxicant where low-level exposure has been tied to significant and permanent harm to children. Both EPA's air quality standard (National Ambient Air Quality Standard –NAAQS) and soil clean-up level are based on concentration-response functions derived from epidemiological studies comparing levels of lead measured in blood with neurodevelopmental outcomes in children at different ages. In both cases, EPA determined that IQ point loss was the most sensitive and robust outcome variable on which to derive the concentration-response function.[18, 19] In 2007, California's Office of Environmental Health Hazard Assessment relied on epidemiological studies to derive a critical effect level which has formed the basis for re-evaluating health-based standards for lead in residential soil and drinking water.[20] This analysis was triggered by findings in epidemiologic studies that neurobehavioral deficits were recorded at levels below the existing regulatory thresholds and concluded that the loss of one IQ point was an appropriate point of departure on

[16] https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0276_summary.pdf.

[17] https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0278_summary.pdf.

[18] EPA 2008. National Ambient Air Quality Standard for Lead – Final Rule.

[19] EPA 1998. RISK ANALYSIS TO SUPPORT STANDARDS FOR LEAD IN PAINT, DUST, AND SOIL (EPA 747-R-97-006). Chapter 4: Dose-response Assessment. https://www.epa.gov/lead/hazard-standard-risk-analysis-tsca-section-403.

[20] CalEPA – OEHHA.2009. Lead Public Health Goal and Soil Level
http://oehha.ca.gov/media/downloads/water/chemicals/phg/leadfinalphg042409_0.pdf
http://oehha.ca.gov/media/downloads/crnr/leadchhsl091709.pdf.

which to derive a blood-lead level of concern.[21] In 2012, the Centers for Disease Control and Prevention relied on epidemiologic data to replace a previous blood lead level of concern of 10 µg/dL with a blood lead action level of 5 µg/dL.[22]

It should be noted that the above examples of use of epidemiologic and biomonitoring data by EPA programs and others are very different from the intentional human dosing studies that have been conducted by pesticide registrants and sometimes used by EPA. An expert workshop of ethicists, physicians, toxicologists, and policy experts hosted by Mount Sinai School of Medicine (2002) reported on several of these intentional-dosing pesticide studies, including this example: "In 1998, after signing a seven-page consent form, dozens of college-age Nebraskans were paid $450 to swallow a pill containing chlorpyrifos. Chlorpyrifos is the active ingredient in Raid roach spray, manufactured by the Dow Chemical Company (Midland, MI). The students learned about this study after reading school newspaper ads urging students to call (402) 474-PAYS to 'earn extra money.'"[23] Indeed, Dow's PBPK model, which is used in the chlorpyrifos assessments, relies on data from deliberate human dosing studies.[24] Prominent scientists and physicians have condemned these pesticide-dosing studies – and EPA's use of them for regulatory decisions - as unethical and bad science.[25]

However, the same experts agree that the use of well-conducted epidemiologic and human biomonitoring studies, from unintentional exposures, can provide useful and important information for risk assessments and regulations. The 2002 Mount Sinai workshop participants recommended that:

Public health scientists and practitioners use biomonitoring information for

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[21] CalEPA – OEHHA 2007. CHILD-SPECIFIC BENCHMARK CHANGE IN BLOOD LEAD CONCENTRATION FOR SCHOOL SITE RISK ASSESSMENT http://oehha.ca.gov/risk-assessment/crnr/final-report-chrc-lead.

[22] In January 2012, an advisory committee recommended the change, based on epidemiologic evidence. *See* Advisory Committee on Childhood Lead Poisoning Prevention of the Centers for Disease Control and Prevention. Low Level Lead Exposure Harms Children: A Renewed Call for Primary Prevention. https://www.cdc.gov/nceh/lead/acclpp/final_document_030712.pdf. In June 2012, the CDC concurred with the advisory committee's recommendation. *See* CDC. Response to Advisory Committee on Childhood Lead Poisoning Recommendations. https://www.cdc.gov/nceh/lead/acclpp/cdc_response_lead_exposure_recs.pdf.

[23] Oleskey C, Fleischman A, Goldman L, Hirschhorn K, Landrigan PJ, Lappé M, Marshall MF, Needleman H, Rhodes R, McCally M. Pesticide testing in humans: ethics and public policy. Environ Health Perspect. 2004 Jun;112(8):914-9. *Available at* https://www.ncbi.nlm.nih.gov/pubmed/15175182.

[24] More detailed comments on the use of human dosing studies are available at Farmworker and Conservation Comments on Chlorpyrifos Revised Human Health Risk Assessment (Apr. 30, 2015) at 36-42, Docket No. EPA-HQ-OPP-2008-0850; *see also supra* note 8.

[25] Sass JB, Needleman HL. Industry testing of toxic pesticides on human subjects concluded "no effect," despite the evidence. Environ Health Perspect. 2004 Mar;112(3):A150-1; author reply A151-2; discussion A152-6, *available at* https://www.ncbi.nlm.nih.gov/pubmed/14998762.

Oleskey C, Fleischman A, Goldman L, Hirschhorn K, Landrigan PJ, Lappé M, Marshall MF, Needleman H, Rhodes R, McCally M. Pesticide testing in humans: ethics and public policy. Environ Health Perspect. 2004 Jun;112(8):914-9, *available at* https://www.ncbi.nlm.nih.gov/pubmed/15175182; Needleman HL, Reigart JR, Landrigan P, Sass J, Bearer C. Benefits and Risks of Pesticide Testing on Humans. *Environmental Health Perspectives*. 2005;113(12):A804-A805, *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1314936/.

tracking, control, and treatment. Biomonitoring data can also play a critical role in identifying novel hazards and high-risk populations, tracking trends in human exposure, and characterizing exposure levels that pose health hazards. Many workshop participants suggested that biomonitoring provides important and useful information for risk assessment, particularly for determining patterns of exposure and the risks that pesticides pose to children's health. Workshop participants agreed that human biomonitoring should be conducted for every pesticide that is currently in use or present in the environment and posing human exposure risks. They also recommended that special consideration be given to assessing the body burdens of pesticides in children. [26]

EPA's use of CCCEH cohort biomonitoring data in its 2016 chlorpyrifos assessment is very much consistent with this recommendation.

2. The CCCEH findings are consistent with a robust body of scientific evidence

The following section is excerpted from comments submitted to the public docket from environmental health scientists and healthcare professionals in support of EPA's 2016 Revised Human Health Risk Assessment and EPA's 2015 proposed tolerance revocation for chlorpyrifos (Sass, Whyatt et al., 2017, 2016):

- Extensive published science from diverse populations correlates pre-natal chlorpyrifos exposure to reduced birth weights, delayed mental and motor development in preschoolers, and reduced IQ and delays in working memory in elementary school children (Rauh et al., 2006, 2011, Whyatt et al., 2005). These persistent neurocognitive findings are especially troubling. In addition, in a pilot study of 6-11 year olds, chlorpyrifos concentrations in umbilical cord blood were associated with changes in brain structure measured by magnetic resonance imaging, including cortical thinning and regional specific cortical deformations (Rauh et al., 2012).

- A 2015 study of inner city minority children reported a link between prenatal exposure and mild to moderate arm tremors measured when the children were middle-school aged, suggesting an even broader scope of effects on the nervous system from early life exposures, and potentially latent or long term neurological damage manifesting a decade later or beyond (Rauh et al., 2015).

- Application of chlorpyrifos to agricultural fields within 1.5 km of the home during pregnancy has also been associated with an increased incidence of autism spectrum disorders in a recent study (Shelton et al., 2014). A recently published study of Costa Rican children living near banana and plantain farms showed a dose-dependent adverse impairment of working memory in boys, oppositional

[26] Oleskey C, Fleischman A, Goldman L, Hirschhorn K, Landrigan PJ, Lappé M, Marshall MF, Needleman H, Rhodes R, McCally M. Pesticide testing in humans: ethics and public policy. Environ Health Perspect. 2004 Jun;112(8):914-9, *available at* https://www.ncbi.nlm.nih.gov/pubmed/15175182.

disorders, ADHD, decreased ability to discriminate colors, and an increased prevalence of cognitive problems in the parents (van Wendel de Joode et al., 2016).

- These epidemiologic results are consistent with data from toxicological studies which found disruption in neuronal development, neurotransmitter systems and synaptic formation as well as behavioral and cognitive impairments in test animals following low-dose perinatal chlorpyrifos exposure (Slotkin 2004; Aldridge et al., 2004, 2005; Slotkin and Seidler, 2005, Levin et al 2001; Roy et al., 2004; Garcia et al., 2002).

- Associations in newborns also were seen between prenatal exposures to organophosphate pesticides generally and abnormalities in primitive reflexes, suggesting an impact on the development of the central nervous system (Engel et al., 2007; Young et al, 2005) and in children with reduction in motor function (Eskenazi et al., 2007; Rauh et al., 2006; Grandjean et al., 2006; Handal et al., 2008; Harari et al., 2010, Rauh et al., 2015), decreases in working and visual memory, processing speed, verbal comprehension, perceptual reasoning, and full scale IQ (Bouchard et al., 2011, Engel et al., 2011, Rauh et al., 2011; Handal et al., 2008) and increases in neuropsychological problems including ADHD, pervasive developmental disorder and behaviors typical of the autism spectrum (Rauh et al., 2006, Marks et al., 2010, Furlong et al., 2014). Certain subpopulations demonstrate greater susceptibility including children of farmworkers (Castorina et al., 2010; Engel et al., 2015) and those who have reduced capacity to detoxify the OPs (Engel et al., 2015).

II. EPA HAS FOUND UNSAFE EXPOSURES FROM FOOD, DRINKING WATER, TOXIC DRIFT, AND WORKER ACTIVITIES, COMPELLING AN IMMEDIATE BAN ON ALL CHLORPYRIFOS USES

In its 2016 Chlorpyrifos Revised Human Health Risk Assessment ("RHHRA"), EPA found that chlorpyrifos presents unacceptable safety risks through exposures from food, drinking water, spray drift, and occupational activities. The risks were found to be particularly alarming for children and farm workers. Under the Federal Food, Drug and Cosmetics Act ("FFDCA"), EPA may not "establish or leave in effect a tolerance for a pesticide chemical residue in or on a food" unless the Administrator determines that the tolerance is safe. 21 U.S.C. § 346a(b)(2)(A)(i). The Food Quality Protection Act ("FQPA"), a 1996 amendment to the FFDCA, requires that EPA make an affirmative determination that there is reasonable certainty of no harm from use of a pesticide in accordance with its label, and it must make this finding considering aggregate and cumulative exposures to infants and children. *Id*. § 346a(b)(2)(C)(ii)(I), (II). EPA must revoke a tolerance if it finds a pesticide residue would not be safe. *Id*. § 346a(b)(2)(A)(i).

Additionally, under the Federal Insecticide, Fungicide and Rodenticide Act ("FIFRA"), a pesticide may not be registered for a food use unless a food tolerance is in place, and whenever a food tolerance is revoked, the registration for use of the pesticide on that food crop must be cancelled. *See* 7 U.S.C. § 136a(c)(5)(D); *see also id*. § 136(bb). Because of this

interdependence, the FQPA directs EPA to coordinate FQPA actions to revoke tolerances with any related, necessary FIFRA action. 21 U.S.C. § 346a(l). Chlorpyrifos fails to meet the FQPA "reasonable certainty of no harm" safety standard, so EPA must revoke all food tolerances and cancel all food uses.

A. EPA Must Revoke All Food Tolerances For Chlorpyrifos Because Dietary Exposures Exceed Safe Levels

Food exposures for chlorpyrifos were found to be unsafe for all population subgroups analyzed, with young children having the highest risks of concern. RHHRA at 23. While the adult subgroup had an alarming risk estimate at 62 times the safe level of exposure, the risk estimate for children ages 1-2 was more than double that of adults at 140 times what EPA deems safe. *Id*.

Additionally, EPA's 2014 Acute and Steady State Dietary (Food Only) Exposure Analysis to Support Registration Review identified extensive use of chlorpyrifos on food crops and widespread contamination in the form of detectable residues.[27] Of particular concern is the frequent detection of residues on fruits consumed regularly by children. Fruits that are a typical part of children's diets – like apples, peaches, oranges and strawberries[28] – are widely grown using chlorpyrifos. Chlorpyrifos residues are found on these fruits, according to the results of USDA Pesticide Data Program (USDA PDP) testing, **even after they are washed and peeled** (in the case of citrus, bananas, and melons). Residues are routinely found on fruits that are not heavily treated with chlorpyrifos in the U.S., due to high consumption of frequently imported fruits, like peaches, grapes, and melons.

Table 2: Chlorpyrifos use and residues on fruit consumed by children

Fruit	Percent of whole fruit (not juice) in kids diet*	Chlorpyrifos residue detected**	Percent of US crop treated with chlorpyrifos**
Apples	36%	Yes	55%
Bananas	13%	Yes	N/A
Melons	11%	Yes	<2.5%
Other fruit/fruit salads	10%	No data	N/A
Citrus	9%	Yes	Oranges - 20%
Berries	8%	Yes	Strawberries - 20%
Peaches/nectarines	7%	Yes	25%/10%
Grapes	5%	Yes	10%

[27] EPA's 2014 Acute and Steady State Dietary (Food Only) Exposure Analysis to Support Registration Review can be found under docket number EPA-HQ-OPP-2008-0850-0197.

[28] Kirsten Herrick *et al., Fruit Consumption by Youth in the United States*, PEDIATRICS, Oct. 2015, *available at* http://pediatrics.aappublications.org/content/pediatrics/136/4/664.full.pdf.

*Source: Herrick et al. 2015. Fruit Consumption by Youth in the United States. *Pediatrics.*
** Source: USEPA 2014. Chlorpyrifos Acute and Steady State Dietary (Food Only) Exposure Analysis to Support Registration Review - Residue testing is on washed and peeled (as applicable) fruit.

USDA's PDP testing prioritizes regular monitoring of pesticide levels on foods with high consumption rates and a focus on foods consumed by children and infants. USDA Pesticide Data Program, Annual Summary – Calendar Year 2015. [29] For this reason, the program regularly tests apples, and other fruit, for residues. EPA's dietary exposure assessment cited USDA PDP residue detections for apples from 2009-2010. The most recent data available from USDA (calendar year 2015) confirms that chlorpyrifos is regularly detected on apples. *Id*. In 2015, residues were also detected on cherries (fresh and frozen), cucumbers, grapes, nectarines, oranges, peaches, pears, potatoes, spinach, strawberries, and tomatoes – nearly 1 in 10 of the peaches sampled were found to have chlorpyrifos residues. *Id*. USDA PDP data confirms the widespread presence of chlorpyrifos residues on fruits and vegetables regularly consumed by children and pregnant women.

Surveys show that apples are regularly consumed by children on a daily basis and EPA's CALENDEX_FCID Profile for children appropriately considers dietary risk from consumption of approximately 1 apple per day.[30, 31] In USDA's PDP testing, the limit of detection for chlorpyrifos on apples ranges from 0.001 – 0.005 ppm. At any level above the detection limit, a child's daily exposure to chlorpyrifos would exceed safe levels.[32] Since USDA PDP data regularly finds detections of chlorpyrifos on apples, and any detection would exceed the steady state Population Adjusted Dose ("ssPAD") due to exposure to apples alone, chlorpyrifos residues on apples present a clear risk to children in the United States. Therefore, EPA cannot set a tolerance that would protect children from the neurodevelopmental risks posed by chlorpyrifos exposures and the tolerances must be revoked immediately.

Apples are not the only commodity of concern. In the 2015 USDA PDP data, the highest chlorpyrifos residue detected was on peaches at 0.38 ppm. Using EPA's standard assumptions for consumption frequency and body weight, exposures to pregnant women (Adult Females 13-49) at this residue level are 413 times safe levels.[33] The frequency and magnitude of chlorpyrifos residues found on highly consumed commodities demonstrates the threat to the safety of the food supply.

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[29] https://www.ams.usda.gov/sites/default/files/media/2015PDPAnnualSummary.pdf.

[30] Herrick *et al*., *supra* note 2.

[31] U.S. EPA, What We Eat in America - Food Commodity Intake Database, http://fcid.foodrisk.org/.

[32] Calculation = 0.001 ug chlorpyrifos/g apples X 182 g apples/day = 0.182 ug chlorpyrifos / 15 kg = 0.012 ug/kg-day which is 700% of the ssPAD only considering exposure from apples.

[33] Calculation = 0.38 ug chlorpyrifos/g peaches X 95.16 g peaches/day = 36.16 ug chlorpyrifos /72.9 kg = 0.496 ug/kg-day which is 41,300% of the ssPAD for Adult Females.

B. Drinking Water Exposures Present Risks of Concern

In its 2014 drinking water assessment, EPA found that many label uses of chlorpyrifos resulted in drinking water contamination levels that exceeded EPA's levels of concern. 80 Fed. Reg. 69,079, 69,083 (Nov. 6, 2015). Total dietary exposure to a pesticide is usually assessed by taking into account combined exposures through food and water. Because in the 2016 RHHRA food exposure alone exceeded target risk levels, any presence of chlorpyrifos in water is unsafe.

EPA finalized a refined drinking water assessment for chlorpyrifos in April 2016, which served to "combine, update and complete the work presented in the 2011 and 2014 drinking water assessments..." 2016 Chlorpyrifos Refined Drinking Water Risk Assessment for Registration Review ("2016 DWA") at 6.[34] The 2016 drinking water assessment results were consistent with the previous assessments and suggested "potential exposure to chlorpyrifos or chlorpyrifos-oxon in finished drinking [sic] based on currently labeled uses." *Id*. Unsurprisingly, higher concentrations of chlorpyrifos and the more potent chlorpyrifos-oxon are likely to be found in areas with higher chlorpyrifos use and areas that are more vulnerable to runoff. *Id*. at 7. Thus, agricultural communities, including farmworkers and their families, are more likely to have their drinking water contaminated by chlorpyrifos. EPA's revised assessment did not result in any changes to its finding that "the majority of estimated drinking water exposures from currently registered uses, including water exposures from non-food uses, continue to exceed safe levels even taking into account more refined drinking water exposures." 81 Fed. Reg. 81,049, 81,050 (Nov. 17, 2016).

It was not possible for EPA to calculate a drinking water level of concern because food exposures alone exceeded risks of concern. However, if one assumed that there are no food exposures to chlorpyrifos, the "no food" drinking water level of concern for infants would be 0.014 ppb (ug/L). RHHRA at 24. In the 2016 Refined Drinking Water Assessment, EPA performed additional analysis to assess potential chlorpyrifos drinking water exposures based on national modeling, regional modeling and monitoring data. All three analyses showed that drinking water concentrations across the country exceed the "no food" drinking water level of concern.

The national-level assessment included both agricultural and non-agricultural (golf course) scenarios. As shown in Table 3 below, surface water sourced estimated drinking water concentrations of chlorpyrifos far exceed the "no food" drinking water level of concern for both the low-end and high-end scenarios by 50 to 12,000-fold.

[34] The 2016 Chlorpyrifos Refined Drinking Water Risk Assessment for Registration Review can be found under docket number EPA-HQ-OPP-2015-0653-0437.

Table 3. Comparison of EPA's national-level estimated chlorpyrifos drinking water concentrations[35] to the "no food" drinking water level of concern.

		1-in-10-year concentration (ug/L)			
	Absolute Peak (ug/L)	**Peak**	**21-day average**	**Annual average**	**30 year annual average (ug/L)**
High end scenario (Michigan tart cherries)	172	129	83.8	39.2	29.7
Exceedance of "no food" drinking water level of concern	**12,286**	**9,214**	**5,986**	**2,800**	**2,121**
Low end scenario (Georgia bulb onions)	8.5	6.2	3.1	1.2	0.8
Exceedance of "no food" drinking water level of concern	**607**	**443**	**221**	**86**	**57**

EPA also completed a regional analysis of all 21 HUC-02 regions in the United States. EPA considers this analysis highly refined and included scenarios to represent agricultural (food and non-food such as Christmas trees), non-agricultural (i.e., golf courses), impervious surface and urban uses. EPA used regionally-specific model inputs, including representative meteorological data from weather stations and application scenarios appropriate to each region.

The regional analysis indicates that all 24 hour and 21-day average estimated concentrations exceed the "no food" drinking water level of concern for all scenarios by 15 - 87,000 fold.[36] EPA's sensitivity analysis indicated that varying standard model inputs would not be expected to change these conclusions. EPA also considered all available water monitoring data. As shown in Table 4 below, bias-factor adjusted chlorpyrifos water concentrations exceed the "no food" drinking water level of concern by 7- 10,500 fold.

[35] From Table 1 of the 2016 Chlorpyrifos Refined Drinking Water Risk Assessment for Registration Review ("2016 DWA") at 7.

[36] Comparison of "food only" drinking water level of concern (0.014 ppb (ug/L) to values in Table 2 of the 2016 DWA at 8-9.

Table 4. Comparison of EPA's bias-factor adjusted estimated chlorpyrifos water concentrations[37] to the "no food" drinking water level of concern.

	Highest measured concentration (ug/L)		Most frequently detected concentrations (ug/L)			
	Unfiltered	**Filtered**	**Unfiltered-low**	**Unfiltered-high**	**Filtered-low**	**Filtered-high**
	147	56.1	0.1	10	0.01	0.1
Exceedance of "no food" drinking water level of concern	**10,500**	**4,007**	**7**	**714**	0.7	**7**

EPA found that the concentrations of chlorpyrifos in water obtained from their modeling analysis corresponded to monitoring data within an order of magnitude, indicating that the models are not overly conservative. In summary, EPA's modeling and monitoring data analysis found that chlorpyrifos drinking water contamination is likely and that such contamination is unsafe.

C. EPA Must Protect Agricultural Communities From Toxic Drift and Other Bystander Exposures

People living in agricultural communities are at particular risk from chlorpyrifos spray drift, especially children who are exposed to drift near their schools and day cares, in their homes, and at playgrounds. Spray buffers are currently in place for chlorpyrifos, but those buffers are far too small to protect people from drift. *See* RHHRA at 30-1. EPA found unsafe levels of chlorpyrifos from the field's edge to distances of more than 300 feet from where the pesticide is sprayed. *Id*. at 31. As with drinking water contamination, farmworkers and their families are disproportionately exposed to toxic chlorpyrifos drift – they are, quite literally, getting hit from all sides. The risks presented by spray drift weigh in favor of a ban on chlorpyrifos, as all uses lead to risks of concern and necessitate buffers in excess of 300 feet.[38]

1. 300 feet buffers do not protect children and pregnant women from unsafe exposures.

EPA analyzed spray drift exposures for adults (dermal only) and children (dermal and incidental oral) resulting from different application methods, on different crop types, and differing application rates at the edge of the field and up to 300 feet away. At the farthest distance evaluated (300 feet from the field), almost all application scenarios resulted in significant risk. When aggregate exposures are considered factoring in inhalation and dietary

[37] From Table 3 of the 2016 DWA at 10.

[38] Indeed, it is unclear how large buffers would actually need to be to adequately protect children because the spray drift modeling does not go beyond 300 feet.

exposures, none of the application scenarios meet the safety standard for bystander exposures. Even at the lowest application rates, aerial and groundboom applications result in estimated exposures for children at 300 feet from the field that are extremely worrisome with all of the margins of exposure ("MOEs") at 10 or below.[39] Given these low MOEs, it would likely require buffer zones much larger than 300 feet to lower exposures to meet the safety standard.

Moreover, these estimates likely do not capture the high-end of the exposure distribution since they are based on an exposure duration of only 1.5 hours per day and do not include inhalation exposures. Given the proximity of homes, schools, parks and playgrounds to fields where chlorpyrifos is applied, there are opportunities for exposure that extend beyond 1.5 hours.

2. Chlorpyrifos levels measured in the air in agricultural communities pose a risk to children and pregnant women.

By evaluating inhalation exposures from chlorpyrifos drift in the 2016 RHHRA, EPA has filled an important exposure gap that was ignored in the 2014 HHRA. Evidence from the multiple air monitoring studies conducted in agricultural communities, summarized in the 2016 RHHRA, show that chlorpyrifos is regularly detected in the ambient air where children and pregnant women are exposed (e.g., in communities and at schools). In addition, research studies have shown that chlorpyrifos is found in the air at considerable distance from where it was applied and persists for multiple days – for example, one study found strong correlations with detections of chlorpyrifos in the air with applications made within 1.5 miles and up to 4 days prior to the sampling event.[40] This is consistent with previous analysis finding that chlorpyrifos detections and air concentrations are correlated with amount of use within a 5 mile (8 km) area around the monitoring site.[41] EPA's evaluation of these studies to consider inhalation exposures is critical to understanding exposures in agricultural communities and should be relied upon.

Even in the absence of comprehensive modeling of volatilization and transport from treated fields under different atmospheric conditions, the ambient monitoring data illustrates that real-world exposures in agricultural communities do not meet the safety standard due to inhalation exposure alone. When aggregate dietary and spray drift exposures are also considered, the risk faced in these communities is staggering. For example, the Shafter Air Monitoring Site is located at a school in close proximity to almond orchards where chlorpyrifos is used. The most recent published data available (2015) from the California Department of Pesticide Regulation ("DPR") showed that chlorpyrifos was detect in nearly two-thirds (61%) of the samples taken at this site.[42] In 2014, the closest field application site was 0.3 miles from the

[39] The margin of exposure in these scenarios must be above 100 to not be of concern.

[40] Harnly, M., McLaughlin, R., Bradman, A., Anderson, M., and Gunier, L. (2005). Correlating Agricultural Use of Organophosphates with Outdoor Air Concentrations: A Particular Concern for Children. Environmental Health Perspective, 113(9): 1184-1189.

[41] Wofford, P., Segawa, R., Schreider, J., Federighi, V., Neal, R., and Brattesani, M. (2014). Community Air Monitoring for Pesticides. Part 3: Using Health-Based Screening Levels to Evaluate Results Collected for a Year. Environ. Monit. Assess., 186(3):1355-1370.

[42] CA DPR. 2016. 2015 Draft Air Monitoring Network Report. http://www.cdpr.ca.gov/docs/emon/airinit/amn_2015_report_draft.pdf.

monitoring site, and a total of 13,837 pounds of chlorpyrifos were used within 5 miles of the monitoring site.[43] EPA's evaluation of the monitoring data from this air monitoring site found both acute and steady-state risks of concern with MOEs below 10. For children attending this school and living nearby, the inhalation exposures are compounded with the potential for spray drift and dietary exposure. In addition, DPR's recent review of the Air Monitoring Network found that almost 30 communities in California were at greater risk of organophosphate drift than Shafter due to the quantity of pesticides applied within 5 miles and meteorological conditions.[44] Given that chlorpyrifos is the dominant organophosphate applied in California fields, it is clear that the inhalation risk EPA found for children and pregnant women at the Shafter site is likely much greater for other communities around the state.

The peak values recorded in all 11 air monitoring data sets result in acute inhalation exposure that do not meet the safety standard for children, and the vast majority do not meet the safety standard for pregnant women. It is clear from this analysis that the levels of chlorpyrifos routinely measured in the air in agricultural communities pose a significant threat to public health.

3. Bystander exposures for children are likely significantly higher than estimates in the 2016 RHHRA due to indoor dust exposures.

The exposure assessment ignored the substantial evidence that chlorpyrifos in indoor dust represents a potentially significant contributor to the total exposure experienced in agricultural communities.[45] Based on exposure models for children 3-5 years of age, dust ingestion was the primary route of exposure to chlorpyrifos among farmworkers' children from an agricultural community in California.[46]

This exposure pathway has been identified in numerous studies conducted in California as well as in Washington State. Although chlorpyrifos breaks down readily when exposed to sunlight and moisture in the outdoor environment, it is known to persist in the indoor environment. Therefore, spray drift deposition that is entrained in dust and blows inside, or is

[43] CA DPR. 2016. Correlating Agricultural Use with Ambient Air Concentrations Of Chlorpyrifos and Chlorpyrifos-Oxon During The Period of 2011-2014. http://www.cdpr.ca.gov/docs/emon/airinit/2560_chlorpyrifos_final.pdf.

[44] DPR presentation on new Air Monitoring Site selection. http://www.cdpr.ca.gov/docs/dept/prec/2016/111816_air_monitoring.pdf.

[45] *See, e.g.*, Brian Curwin et al., "Pesticide Contamination Inside Farm and Nonfarm Homes," *Journal of Occupational and Environmental Hygiene* 2, no. 7 (July 2005): 357–67; Brian Curwin et al., "Urinary Pesticide Concentrations Among Children, Mothers and Fathers Living in Farm and Non-Farm Households in Iowa," *Annals of Occupational Hygiene* 51, no. 1 (June 23, 2006): 53–65; Martha Harnly et al., "Pesticides in Dust from Homes in an Agricultural Area," *Environmental Science & Technology* 43, no. 23 (Dec. 2009): 8767–74; Richard Fenske et al., "Breaking the Take Home Pesticide Exposure Pathway for Agricultural Families: Workplace Predictors of Residential Contamination," *American Journal of Industrial Medicine* 56, no. 9 (Sept. 2013): 1063–71; Beti Thompson et al., "Variability in the Take-Home Pathway: Farmworkers and Non-Farmworkers and Their Children," *Journal of Exposure Science and Environmental Epidemiology* 24, no. 5 (Sept. 2014): 522–31.

[46] Paloma Beamer et al., "Relative Pesticide and Exposure Route Contribution to Aggregate and Cumulative Dose in Young Farmworker Children." *International Journal of Environmental Research and Public Health* 9, no. 1 (January 3, 2012): 73–96.

brought indoors by workers who take it home on their clothes and boots, can represent a critical route of exposure, particularly for young children.

In Washington State, several studies have documented evidence supporting the take-home pathway. In one study, chlorpyrifos house dust concentrations were found to be elevated in agricultural (farmworker) family homes located more than ¼ mile from farmland, and chlorpyrifos residues were detected on parents' work boots and children's hands for many of the agricultural families.[47] In this study, common practices among workers likely contributed to pesticide concentrations in dust because most workers did not change out of work clothes or boots before leaving the workplace and stored work clothes and boots at home. More than 2/3 of workers did not have laundry facilities in their homes and most wore both work clothes and work boots into their homes. In another study in Washington State, chlorpyrifos residues were found on the hands and toys of children living in agricultural communities, and chlorpyrifos was found in half of the indoor air samples taken.[48]

D. A Ban on Chlorpyrifos is Necessary to Protect Workers.

Concerning risks to workers, EPA found that even with maximum levels of personal protective equipment or engineering controls, *all* agricultural occupational handler scenarios, primary seed treatment handler scenarios, and secondary seed treatment scenarios expose workers to unsafe levels of chlorpyrifos. RHHRA at 36-7. Indeed, the harm faced by occupational handlers is perhaps understated by simply referring to the exposures as unsafe given that, in all agricultural scenarios, the level of concern is exceeded by several orders of magnitude. *See id.*, Appendix E, Chlorpyrifos Occupational Handler Risk Estimates. The margin of exposure in these scenarios must be more than 100 to not be of concern, and in the airblast applicator scenario for California and Arizona citrus, for example, the combined (dermal and inhalation) margin of exposure is 0.0092. Moreover, even though current labels allow workers to re-enter the fields within 1-5 days after pesticide spraying, EPA found that, on average, re-entry intervals of at least 18 days were needed to protect workers from risks of concern. RHHRA at 38. Because there are no scenarios in which chlorpyrifos can be safely handled, a ban on the pesticide is the only way to protect workers.

III. THE TOLERANCE REVOCATIONS AND CANCELLATIONS SHOULD BE EFFECTIVE WITHIN MONTHS OF THE DETERMINATION BECAUSE OF THE IRREPARABLE HARM FROM UNSAFE CHLORPYRIFOS EXPOSURES

EPA must act quickly to revoke all tolerances for chlorpyrifos based on its findings of woefully unsafe exposures from food, drinking water, spray drift, and occupational activities. While the 2016 RHHRA more accurately illustrates the risks presented by chlorpyrifos for reasons stated above, it is worth noting that EPA initially proposed revocation of all chlorpyrifos food tolerances based on its conclusions from the 2014 Chlorpyrifos RHHRA, which used the under-protective regulatory endpoint of 10% cholinesterase inhibition. *See* 80 Fed. Reg. at

[47] Richard Fenske et al., "Children's Exposure to Chlorpyrifos and Parathion in an Agricultural Community in Central Washington State." *Environmental Health Perspectives* 110, no. 5 (May 2002): 549–53.

[48] Chensheng Lu et al., "Multipathway Organophosphorus Pesticide Exposures of Preschool Children Living in Agricultural and Nonagricultural Communities." *Envtl. Research* 96, no. 3 (Nov. 2004): 283–89.

69,081 (EPA was "unable to conclude that the risk from aggregate exposure from the use of chlorpyrifos meets the safety standard of the Federal Food, Drug, and Cosmetic Act (FFDCA)"). The 2016 RHHRA serves to reinforce EPA's previous conclusion that uses of chlorpyrifos do not meet the FFDCA/FQPA safety standard. A ban on all food uses of chlorpyrifos must necessarily follow. Furthermore, the grave risks associated with chlorpyrifos exposure offer strong support for an effective date not more than six months from the date of the revocation determination.

Since October 2015, when EPA proposed revoking all food tolerances for chlorpyrifos, the European Union agreed upon new, more protective endpoints following an updated toxicological review of chlorpyrifos.[49] As a result of these new endpoints, the United Kingdom banned all but one use of chlorpyrifos and took swift action to protect its citizens from the pesticide. The United Kingdom announced its ban in February 2016, and uses of chlorpyrifos, including those of existing stocks, had to end by April 2016.[50] Because no safe uses have been identified since EPA proposed revocation over a year ago, EPA should act with similar haste to ban all uses of chlorpyrifos and protect people, particularly children and farm workers, from irreparable harm.

A. A Ban is Necessary to Protect Children from the Developmental Delays and Learning Disabilities Correlated with Chlorpyrifos Exposure

The 2016 RHHRA appropriately used a regulatory endpoint based on neurodevelopmental harms associated with *in utero* chlorpyrifos exposure. The types of neurodevelopmental impacts correlated with exposure to chlorpyrifos and other organophosphates are every parent's nightmare. Every parent watches with wonder as their children start to crawl and walk, yet chlorpyrifos has delayed motor development. Parents marvel as their children start to learn, yet chlorpyrifos reduces working memory and IQ.

Chlorpyrifos is also associated with learning disabilities like attention deficit disorders that seem to be reaching epidemic proportions. These types of learning disabilities frustrate and impair the child's growth and well-being, and necessitate substantial societal investments in education, accommodations, and behavior management. Individual and societal harms have been well-studied and even quantified in connection with chemicals like lead, and federal agencies, including EPA, have found regulation to prevent exposures to such chemicals cost-effective.[51]

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[49] Commission Regulation 2016/60, 2016 O.J. (L 14) 1 (EU), *available at* http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0060&rid=2.

[50] HEALTH AND SAFETY EXECUTIVE, CHANGES TO AUTHORISATIONS FOR PRODUCTS CONTAINING CHLORPYRIFOS, E-BULLETIN, 2016 (U.K.), *available at* http://www.hse.gov.uk/pesticides/news/information-update-0316.htm.

[51] *See, e.g.*, Declaration of Philip J. Landrigan, ¶¶ 33-6 (Attachment 2).

B. EPA Must Take Quick Action to Protect Farmworkers and Their Families Who are Disproportionately Harmed by Chlorpyrifos Exposure

EPA has recognized that pesticides disproportionately cause harm to farmworkers and their families, who are predominantly poor and majority Latino. 79 Fed. Reg. 15,452 (March 19, 2014). Farmworkers frequently experience acute poisoning from chlorpyrifos exposure. While there is no nationwide reporting system for pesticide poisoning incidents, every year the California and Washington incident reporting systems are filled with reports of worker poisonings from chlorpyrifos. Moreover, poisoning incidents are underreported due to fear of retaliation, reluctance to seek medical care, misdiagnoses, and other disincentives to report.[52] These poisonings take their toll. Workers describe the onset of severe headaches and body-wrenching flu symptoms that sometimes lead to seizures, blackouts, and worse. Many workers report heightened sensitivities to pesticide illnesses that persist, and some have long-lasting neurological impacts. When workers become sick, there are societal costs as well. Workers often become unproductive, miss work, or need to seek medical care, which may be covered by workers' compensation, other public health systems, or at the workers' expense.

Not only are farmworkers exposed to undue risk of chlorpyrifos poisoning on the job, they and their families are more likely to be harmed by toxic pesticide drift and drinking water contamination in the places where they live. For instance, air monitoring conducted in 2004 and 2005 in the agricultural community of Lindsay, California, found chlorpyrifos in the air at levels far exceeding the level of concern for children even when using the prior, less protective endpoint.[53] As to drinking water contamination, EPA's 2016 drinking water assessment noted that higher concentrations of chlorpyrifos and chlorpyrifos-oxon are likely to be found in areas with higher chlorpyrifos use, such as agricultural communities. *See* DWA at 7. Executive Order 12898 on environmental justice requires EPA to identify and take steps to prevent these kinds of disproportionate pollution burdens. Exec. Order No. 12,898, 59 Fed. Reg. 7629 (Feb. 16, 1994). Thus far, EPA has failed to meet this requirement, leaving farm workers and their families grossly underprotected from a toxic pesticide that causes, among other serious harms, permanent brain damage in children. EPA must act quickly to alleviate this burden, which can only be accomplished by a swift ban on all food uses of chlorpyrifos.

CONCLUSION

EPA must act expeditiously to revoke all food tolerances and cancel all food uses for chlorpyrifos. Even when using the wrong endpoint of 10% cholinesterase inhibition, EPA found that aggregate exposures to chlorpyrifos did not meet the FQPA safety standard and proposed revocation of all food tolerances. Using the appropriate endpoint of neurodevelopmental effects, EPA found that food exposures alone exceed safe levels, especially for young children. A ban on all food uses of chlorpyrifos is the only defensible next step, and an effective date of not more

[52] EPA has acknowledged the underreporting of pesticide poisoning incidents and assumes that only 25% of acute incidents are reported. Worker Protection Standard Revisions, 79 Fed. Reg. 15,444, 15,453, 15,459 (Mar. 19, 2014).

[53] Katherine Mills and Susan Kegley, Pesticide Action Network North America, "Air Monitoring for Chlorpyrifos in Lindsay, California" (July 14, 2006).

than six months from the date of the revocation determination is necessary based on the grave risk of harm, particularly to farmworkers and their families.

Respectfully submitted,

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BILLING CODE 6560-50-P

ENVIRONMENTAL PROTECTION AGENCY

[EPA-HQ-OPP-2007-1005; FRL-9960-77]

Chlorpyrifos; Order Denying PANNA and NRDC's Petition to Revoke Tolerances

AGENCY: Environmental Protection Agency (EPA).

ACTION: Order.

SUMMARY: In this Order, EPA denies a petition requesting that EPA revoke all tolerances for the pesticide chlorpyrifos under section 408(d) of the Federal Food, Drug, and Cosmetic Act and cancel all chlorpyrifos registrations under the Federal Insecticide, Fungicide and Rodenticide Act. The petition was filed in September 2007 by the Pesticide Action Network North America (PANNA) and the Natural Resources Defense Council (NRDC).

DATES: This Order is effective [*insert date of publication in the **Federal Register***]. Objections and requests for hearings must be received on or before [*insert date 60 days after date of publication in the **Federal Register***], and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Unit I. of the **SUPPLEMENTARY INFORMATION**.)

ADDRESSES: The docket for this action, identified by docket identification (ID) number EPA-HQ-OPP-2007-1005, is available at *http://www.regulations.gov* or at the Office of Pesticide Programs Regulatory Public Docket (OPP Docket) in the Environmental Protection Agency Docket Center (EPA/DC), West William Jefferson Clinton Bldg., Rm. 3334, 1301 Constitution Ave., NW., Washington, DC 20460-0001. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday,

excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the OPP Docket is (703) 305-5805. Please review the visitor instructions and additional information about the docket available at *http://www.epa.gov/dockets*.

FOR FURTHER INFORMATION CONTACT: Pesticide Re-Evaluation Division (7508P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; telephone number: (703) 347-0206; email address: *OPPChlorpyrifosInquiries@epa.gov*.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

In this document EPA denies a petition by PANNA and the NRDC to revoke pesticide tolerances and cancel pesticide registrations. This action may also be of interest to agricultural producers, food manufacturers, or pesticide manufacturers. Potentially affected entities may include, but are not limited to those engaged in the following activities:

- Crop production (North American Industrial Classification System (NAICS) code 111), e.g., agricultural workers; greenhouse, nursery, and floriculture workers; farmers.
- Animal production (NAICS code 112), e.g., cattle ranchers and farmers, dairy cattle farmers, livestock farmers.
- Food manufacturing (NAICS code 311), e.g. agricultural workers; farmers; greenhouse, nursery, and floriculture workers; ranchers; pesticide applicators.

- Pesticide manufacturing (NAICS code 32532), e.g. agricultural workers; commercial applicators; farmers, greenhouse, nursery, and floriculture workers; residential users.

This listing is not intended to be exhaustive, but rather to provide a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in this unit could also be affected. The NAICS codes have been provided to assists you and others in determining whether this action might apply to certain entities. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

B. How Can I Get Copies of This Document and Other Related Information?

EPA has established a docket for this action under Docket ID No. EPA-HQ-OPP-2007-1005. Additional information relevant to this action is located in the chlorpyrifos registration review docket under Docket ID No, EPA-HQ-OPP-2008-0850 and the chlorpyrifos tolerance rulemaking docket under Docket ID No, EPA-HQ-OPP-2015-0653. To access the electronic docket, go to *http://www.regulations.gov*, select "Advanced Search," then "Docket Search." Insert the docket ID number where indicated and select the "Submit" button. Follow the instructions on the regulations.gov website to view the docket index or access available documents. All documents in the docket are listed in the docket index available in regulations.gov. Although listed in the index, some information is not publicly available, e.g., Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available in the electronic

docket or, if only available in hard copy, at the OPP Regulatory Public Docket in Rm. S-4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. The Docket Facility is open from 8:30 a.m. to 4 p.m. Monday through Friday, excluding legal holidays. The Docket Facility telephone number is (703) 305-5805.

C. Can I File an Objection or Hearing Request?

Under section 408(g) of the Federal Food, Drug and Cosmetic Act (FFDCA) (21 U.S.C. 346a(g)), any person may file an objection to any aspect of this order and may also request a hearing on those objections. You must file your objection or request a hearing on this order in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA-HQ-OPP-2007-1005 in the subject line on the first page of your submission. All objections and requests for a hearing must be in writing, and must be received by the Hearing Clerk on or before [*insert date 60 days after date of publication in the* **Federal Register**], and may be submitted by one of the following methods:

• *Mail*:. U.S. EPA Office of Administrative Law Judges, Mailcode 1900R, 1200 Pennsylvania Ave., NW., Washington, DC 20460

• *Hand Delivery*: U.S. Environmental Protection Agency Office of Administrative Law Judges, Ronald Reagan Building, Rm. M1200, 1300 Pennsylvania Ave., NW., Washington, DC 20004. Deliveries are only accepted during the Office's normal hours of operation (8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays). Special arrangements should be made for deliveries of boxed information. The Office's telephone number is (202) 564-6255.

In addition to filing an objection or hearing request with the Hearing Clerk as

described in 40 CFR part 178, please submit a copy of the filing that does not contain CBI for inclusion in the public docket that is described in I.B.1 above. Information not marked confidential pursuant to 40 CFR part 2 may be disclosed publicly by EPA without prior notice. Submit this copy, identified by docket ID number EPA-HQ-OPP-2007-1005, by one of the following methods:

- *Federal eRulemaking Portal*: *http://www.regulations.gov*. Follow the on-line instructions for submitting comments.

- *Mail*: U.S. Environmental Protection Agency Office of Pesticide Programs (OPP) Public Regulatory Docket (7502P), 1200 Pennsylvania, Ave., NW, Washington DC 20460-0001.

- *Delivery*: OPP Regulatory Public Docket (7502P), Environmental Protection Agency, Rm. S-4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. Deliveries are only accepted during the Docket's normal hours of operation (8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays). Special arrangements should be made for deliveries of boxed information. The Docket Facility telephone number is (703) 305-5805.

D. What Should be Included in Objections?

The objection stage is the second stage in the petition process under FFDCA section 408. This multi-stage process is initiated by a petition requesting establishment, modification, or revocation of a tolerance. Once EPA makes a decision on a petition, and publishes its decision in the Federal Register, the second stage of the petition process is triggered. At this point, parties who disagree with EPA's decision, whether it is a decision to grant or deny the petition, may file objections with EPA to the decision made.

The objection stage gives parties a chance to seek review of EPA's decision before the Agency. This is an opportunity for parties to contest the conclusions EPA reached and the determinations underlying those conclusions. As an administrative review stage, it is not an opportunity to raise new issues or arguments or present facts or information that were available earlier. On the other hand, parties must do more than repeat the claims in the petition. The objection stage is the opportunity to challenge EPA's decision on the petition. An objection fails on its face if it does not identify aspects of EPA's decision believed to be in error and explain the reason why EPA's decision is incorrect. This two-stage process insures that issues are fully aired before the Agency and a comprehensive record is compiled, prior to judicial review.

II. Introduction

A. What Action is the Agency Taking?

In this document, EPA denies a petition by PANNA and the NRDC. In a petition dated September 12, 2007, PANNA and NRDC (the petitioners) requested that EPA revoke all tolerances for the pesticide chlorpyrifos established under section 408 of the FFDCA. (Ref. 1) The petition also sought the cancellation of all chlorpyrifos pesticide product registrations under section 6 the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), 7 U.S.C. 136d. The PANNA and NRDC petition (the Petition) raised the following claims regarding EPA's reregistration and active registrations of chlorpyrifos in support of the request for tolerance revocation and product cancellation:

1. EPA has ignored genetic evidence of vulnerable populations.
2. EPA has needlessly delayed a decision regarding endocrine disrupting effects.
3. EPA has ignored data regarding cancer risks.

4. EPA's 2006 cumulative risk assessment (CRA) for the organophosphates misrepresented risks and failed to apply FQPA 10X safety factor. [For convenience's sake, the legal requirements regarding the additional safety margin for infants and children in section 408(b)(2)(C) of the FFDCA are referred to throughout this response as the "FQPA 10X safety factor" or simply the "FQPA safety factor." Due to Congress' focus on both pre- and post-natal toxicity, EPA has interpreted this additional safety factor as pertaining to risks to infants and children that arise due to pre-natal exposure as well as to exposure during childhood years.]

5. EPA has over-relied on registrant data.

6. EPA has failed to properly address the exporting hazard in foreign countries from chlorpyrifos.

7. EPA has failed to quantitatively incorporate data demonstrating long-lasting effects from early life exposure to chlorpyrifos in children.

8. EPA has disregarded data demonstrating that there is no evidence of a safe level of exposure during pre-birth and early life stages.

9. EPA has failed to cite or quantitatively incorporate studies and clinical reports suggesting potential adverse effects below 10% cholinesterase inhibition.

10. EPA has failed to incorporate inhalation routes of exposure.

In this order EPA is denying the Petition in full. EPA provided the petitioners with two interim responses on July 16, 2012, and July 15, 2014, respectively. The July 16, 2012, response denied claim 6 (export hazard) completely and that portion of the response was a final agency action. The remainder of the July 16, 2012, response and the July 15, 2014, response expressed EPA's intention to deny six other petition claims (1-5

and 10). [In the 2012 response, EPA did, however, inform petitioners of its approval of label mitigation (in the form of rate reductions and spray drift buffers) to reduce bystander risks, including risks from inhalation exposure, which in effect partially granted petition claim 10.] EPA made clear in both the 2012 and 2014 responses that, absent a request from petitioners, EPA's denial of those six claims would not be made final until EPA finalized its response to the entire Petition. Petitioners made no such request. EPA is finalizing its denial of those six claims in this order.

The remaining claims (7-9) all related to same issue: whether the potential exists for chlorpyrifos to cause neurodevelopmental effects in children at exposure levels below EPA's existing regulatory standard (10% cholinesterase inhibition). While these claims raised novel, highly complex and unresolved scientific issues, EPA decided it would nonetheless expedite the registration review of chlorpyrifos under FIFRA section 3(g), and attempt to address these issues several years in advance of the October 1, 2022 deadline for completing that review. Accordingly, EPA also decided as a policy matter that it would address the Petition claims raising these matters on a similar timeframe. Although EPA had expedited its registration review to address these issues, the petitioners were not satisfied with EPA's progress in responding to the Petition and they brought legal action in the 9th Circuit Court of Appeals to compel EPA to either issue an order denying the Petition or to grant the Petition by initiating the tolerance revocation process. In August 2015, the 9th Circuit issued a ruling in favor of the petitioners and ordered EPA to respond to the Petition by either denying the Petition or issuing a proposed or final rule revoking chlorpyrifos tolerances. *In re Pesticide Action Network of North America v. EPA*, 798 F.3d (9th Cir. 2015).

On November 6, 2015, pursuant to the 9th Circuit's order, EPA proposed to revoke all chlorpyrifos tolerances based in part on uncertainty surrounding the potential for chlorpyrifos to cause neurodevelopmental effects – the issue raised in petition claims 7-9. Following publication of the proposal, the 9th Circuit announced that it would retain jurisdiction over this matter and on August 12, 2016, the court further ordered EPA to complete a final petition response by March 31, 2017 and made clear that no further extensions would be granted. On November 17, 2016, EPA published a notice of data availability that released for public comment EPA's revised risk assessment that proposed a new regulatory point of departure based on the potential for chlorpyrifos to result in adverse neurodevelopmental effects.

Following a review of comments on both the November 2015 proposal and the November 2016 notice of data availability, EPA has concluded that, despite several years of study, the science addressing neurodevelopmental effects remains unresolved and that further evaluation of the science during the remaining time for completion of registration review is warranted to achieve greater certainty as to whether the potential exists for adverse neurodevelopmental effects to occur from current human exposures to chlorpyrifos. EPA has therefore concluded that it will not complete the human health portion of the registration review or any associated tolerance revocation of chlorpyrifos without first attempting to come to a clearer scientific resolution on those issues. As noted, Congress has provided that EPA must complete registration review by October 1, 2022. Because the 9th Circuit's August 12, 2016 order has made clear, however, that further extensions to the March 31, 2017 deadline for responding to the Petition would not be granted, EPA is today also denying all remaining petition claims.

B. What Is the Agency's Authority for Taking This Action?

Under section 408(d)(4) of the FFDCA, EPA is authorized to respond to a section 408(d) petition to revoke tolerance either by issuing a final rule revoking the tolerances, issuing a proposed rule, or issuing an order denying the Petition.

III. Statutory and Regulatory Background

A. FFDCA/FIFRA and Applicable Regulations

1. *In general.* EPA establishes maximum residue limits, or ''tolerances,'' for pesticide residues in food and feed commodities under section 408 of the FFDCA. Without such a tolerance or an exemption from the requirement of a tolerance, a food containing a pesticide residue is ''adulterated'' under section 402 of the FFDCA and may not be legally moved in interstate commerce. Section 408 was substantially rewritten by the Food Quality Protection Act of 1996 (FQPA) (Public Law 104–170, 110 Stat. 1489 (1996)), which established a detailed safety standard for pesticides and integrated EPA's regulation of pesticide food residues under the FFDCA with EPA's registration and re-evaluation of pesticides under FIFRA. The standard for issuing or maintaining a tolerance under section 408(b)(2)(A)(i) of the FFDCA is whether it is ''safe.'' ''Safe'' is defined by section 408(b)(2)(A)(ii) to mean that ''there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.''

While the FFDCA authorizes the establishment of legal limits for pesticide residues in food, section 3(a) of FIFRA requires the approval of pesticides prior to their

sale and distribution, and establishes a registration regime for regulating the use of pesticides. FIFRA regulates pesticide use in conjunction with its registration scheme by requiring EPA review and approval of pesticide labels and specifying that use of a pesticide inconsistent with its label is a violation of federal law. In the FQPA, Congress integrated action under the two statutes by requiring that the safety standard under the FFDCA be used as a criterion in FIFRA registration actions as to pesticide uses which result in dietary risk from residues in or on food, (*see* FIFRA section 2(bb)), and directing that EPA coordinate, to the extent practicable, revocations of tolerances with pesticide cancellations under FIFRA. (*see* FFDCA section 408(l)(1)). Under section 3(g) of FIFRA, EPA is required to re-evaluate pesticides under the FIFRA standard – which includes a determination regarding the safety of existing FFDCA tolerances – every 15 years under a program known as "registration review." The deadline for completing the registration review for chlorpyrifos is October 1, 2022.

2. *Procedures for establishing, amending, or revoking tolerances*. Tolerances are established, amended, or revoked by rulemaking under the unique procedural framework set forth in the FFDCA. Generally, a tolerance rulemaking is initiated by the party seeking to establish, amend, or revoke a tolerance by means of filing a petition with EPA. (*See* FFDCA section 408(d)(1)). EPA publishes in the **Federal Register** a notice of the petition filing and requests public comment. After reviewing the petition, and any comments received on it, section 408(d)(4) provides that EPA may issue a final rule establishing, amending, or revoking the tolerance, issue a proposed rule to do the same, or deny the petition.

Once EPA takes final action on the petition by establishing, amending, or

revoking the tolerance or denying the petition, section 408(g)(2) allows any party to file objections with EPA and seek an evidentiary hearing on those objections. Objections and hearing requests must be filed within 60 days. Section 408(g)(2)(B) provides that EPA shall ''hold a public evidentiary hearing if and to the extent the Administrator determines that such a public hearing is necessary to receive factual evidence relevant to material issues of fact raised by the objections.'' EPA regulations make clear that hearings will only be granted where it is shown that there is ''a genuine and substantial issue of fact,'' the requestor has identified evidence 'which "would, if established, resolve one or more of such issues in favor of the requestor,'' and the issue is ''determinative'' with regard to the relief requested. (40 CFR 178.32(b)). Further, a party may not raise issues in objections unless they were part of the petition and an objecting party must state objections to the EPA decision and not just repeat the allegations in its petition. *Corn Growers v. EPA*, 613 F.2d 266 (D.C. Cir. 2010), cert. denied, 131 S. Ct. 2931 (2011). EPA's final order on the objections is subject to judicial review. (21 U.S.C. 346a(h)(1)).

IV. Chlorpyrifos Regulatory Background

Chlorpyrifos (0,0-diethyl-0-3,5,6-trichloro-2-pyridyl phosphorothioate) is a broad-spectrum, chlorinated organophosphate (OP) insecticide that has been registered for use in the United States since 1965. By pounds of active ingredient, it is the most widely used conventional insecticide in the country. Currently registered use sites include a large variety of food crops (including tree fruits and nuts, many types of small fruits and vegetables, including vegetable seed treatments, grain/oilseed crops, and cotton, for example), and non-food use settings (e.g., ornamental and agricultural seed production, non-residential turf, industrial sites/rights of way, greenhouse and nursery production,

sod farms, pulpwood production, public health and wood protection). For some of these crops, chlorpyrifos is currently the only cost-effective choice for control of certain insect pests. In 2000, the chlorpyrifos registrants reached an agreement with EPA to voluntarily cancel all residential use products except those registered for ant and roach baits in child-resistant packaging and fire ant mound treatments.

In 2006, EPA completed FIFRA section 4 reregistration and FFDCA tolerance reassessment for chlorpyrifos and the OP class of pesticides. Having completed reregistration and tolerance reassessment, EPA is required to complete the next re-evaluation of chlorpyrifos under the FIFRA section 3(g) registration review program by October 1, 2022. Given ongoing scientific developments in the study of the OPs generally, in March 2009 EPA announced its decision to prioritize the FIFRA section 3(g) registration review of chlorpyrifos by opening a public docket and releasing a preliminary work plan to complete the chlorpyrifos registration review by 2015 – 7 years in advance of the date required by law.

The registration review of chlorpyrifos and the OPs has presented EPA with numerous novel scientific issues that the agency has taken to multiple FIFRA Scientific Advisory Panel (SAP) meetings since the completion of reregistration. [The SAP is a federal advisory committee created by section 25(d) of FIFRA, that serves as EPA's primary source of peer review for significant regulatory and policy matters involving pesticides.] Many of these complex scientific issues formed the basis of the 2007 petition filed by PANNA and NRDC and EPA therefore decided to address the Petition on a similar timeframe to EPA's expedited registration review schedule.

Although EPA expedited the chlorpyrifos registration review in an attempt to

address the novel scientific issues raised by the Petition in advance of the statutory deadline, the petitioners were dissatisfied with the pace of EPA's response efforts and have sued EPA in federal court on three separate occasions to compel a faster response to the Petition. As explained in Unit V., EPA had addressed 7 of the 10 claims asserted in the Petition by either denying the claim, issuing a preliminary denial or approving label mitigation to address the claims, but on June 10, 2015, in the *PANNA* decision, the U.S. Court of Appeals for the Ninth Circuit signaled its intent to order EPA to complete its response to the Petition and directed EPA to inform the court how – and by when – EPA intended to respond. On June 30, 2015, EPA informed the court that it intended to propose by April 15, 2016, the revocation of all chlorpyrifos tolerances in the absence of pesticide label mitigation that ensures that exposures will be safe. On August 10, 2015, the court rejected EPA's time line and issued a mandamus order directing EPA to "issue either a proposed or final revocation rule or a full and final response to the administrative Petition by October 31, 2015."

On October 30, 2015, EPA issued a proposed rule to revoke all chlorpyrifos tolerances which it published in the Federal Register on November 6, 2015 (80 FR 69080). On December 10, 2015, the Ninth Circuit issued a further order requiring EPA to complete any final rule (or petition denial) and fully respond to the Petition by December 30, 2016. On June 30, 2016, EPA sought a 6-month extension to that deadline in order to allow EPA to fully consider the most recent views of the FIFRA SAP with respect to chlorpyrifos toxicology. The FIFRA SAP report was finalized and made available for EPA consideration on July 20, 2016. (Ref. 2) On August 12, 2016, the court rejected EPA's request for a 6-month extension and ordered EPA to complete its final action by

March 31, 2017 (effectively granting EPA a three-month extension). On November 17, 2016, EPA published a notice of data availability (NODA) seeking public comment on both EPA's revised risk and water assessments and reopening the comment period on the proposal to revoke all chlorpyrifos (81 FR 81049). The comment period for the NODA closed on January 17, 2017.

V. Ruling on Petition

This order denies the Petition on the nine remaining grounds for which EPA has not issued a final denial that can be the subject of objections under section 408(g)(2) of the FFDCA. As noted in Unit II, on July 16, 2012, EPA denied as final agency action petitioners' claim 6 that the registration of chlorpyrifos created an export hazard for workers in foreign countries. That response and the response of July 15, 2014, also included EPA's preliminary denial of petition claims 1-5 and 10 (except to the extent EPA granted that claim) and EPA's responses to those claims are now incorporated into this order as set forth below. This unit also includes EPA's basis for denying petition claims 7-9. Each specific petition claim is summarized in this Unit V. immediately prior to EPA's response to the claim.

1. Genetic Evidence of Vulnerable Populations

a. Petitioners' claim. Petitioners claim that as part of EPA's reregistration decision (which was completed in 2006 with the completion of the organophosphate cumulative risk assessment) the Agency failed to calculate an appropriate intra-species uncertainty factor (i.e., within human variability) for chlorpyrifos in both its aggregate and cumulative risk assessments (CRA). They assert that certain relevant, robust data, specifically the Furlong et al. (2006) study (Ref. 3) that addresses intra-species variability

in the behavior of the detoxifying enzyme paraoxonase (PON1), indicate that the Agency should have applied an intra-species safety factor "of at least 150X in the aggregate and cumulative assessments" rather than the 10X factor EPA applied. Petitioners conclude by noting that applying an intra-species factor of 100X or higher would require setting tolerances below the level of detection, which therefore should compel EPA to revoke all chlorpyrifos tolerances.

b. *Agency Response.* Petitioners are correct that the Agency, as part of the 2006 OP CRA, evaluated, but did not rely on Furlong et al. in setting the intra-species uncertainty factor for that assessment. The Agency did not rely on the results of the PON1 data in the OP CRA because these data do not take into consideration the complexity of OP metabolism, which involves multiple metabolic enzymes, not just PON1. In addition, EPA believes the methodology utilized in the Furlong et al. study to measure intra-species variability – i.e., combining values from multiple species (transgenic mice and human) to determine the range of sensitivity within a single species – is not consistent with well-established international risk assessment practices. Further, EPA believes that petitioners' assertion that the Furlong et al. study supports an intra-species uncertainty factor of at least 150X is based on an analysis of the data that is inconsistent with EPA policy and widely- accepted international guidance on the development of intra-species uncertainty factors. In addition, the 2008 FIFRA SAP did not support the use of the Furlong et al (2006) study alone in deriving an intra-species factor. For these reasons, and as further explained below, EPA believes it is not appropriate to solely rely on the results of the Furlong et al. study, or petitioners' interpretation of those results, for purposes of determining the intra-species uncertainty

factor. To determine that factor, EPA first uses science tools to quantitatively characterize human variability in both exposure and dosimetry, and then determines the appropriate intra-species uncertainty factor to protect sensitive populations. Specifically, for chlorpyrifos, EPA uses a physiologically-based pharmacokinetic (PBPK) model to account for human variability in the absorption, distribution, metabolism and excretion (ADME) of chemicals based on key physiological, biochemicals, and physicochemical determinants of these ADME processes, including the influence of PON1 variability.

Addressing human variability and sensitive populations is an important aspect of the Agency's risk assessment process. The Agency is well aware of the issue of PON1 and has examined the scientific evidence on this source of genetic variability. PON1 is one of the key detoxification enzymes of chlorpyrifos and is included as part of the PBPK model used by EPA in the 2014 human health risk assessment (HHRA) and 2016 revised risk assessment. Specifically, PON1 is an A-esterase which can metabolize chlorpyrifos-oxon without inactivating the enzyme. (Ref. 4) Indeed, as part of the 2008 SAP, EPA performed a literature review of PON1 and its possible use in informing the intra-species (i.e., within human variability) uncertainty factor. This literature review can be found in the draft Appendix E: Data Derived Extrapolation Factor Analysis to the draft Science Issue Paper: Chlorpyrifos Hazard and Dose Response Characterization.(Ref. 5) In sum, the Agency considered available PON1 data from more than 25 studies from diverse human populations worldwide.

The Agency focused on the PON1-192 polymorphism since it has been linked to chlorpyrifos-oxon sensitivity in experimental toxicology studies and, has been evaluated in epidemiology studies attempting to associate PON1 status with health outcomes

following OP pesticide exposure in adults and children (Holland et al., 2006; Chen et al., 2003. (Ref. 6). [Note, Holland et al (2006) and Furlong et al (2006) report findings from the same cohort. The Holland reference provides enzymes activities for specific polymorphisms in Table 4; the Furlong paper does not report such values and provides information primarily in graphical form.] However, EPA believes that focusing on PON1 variability in isolation from other metabolic action is not an appropriate approach for developing a data-driven uncertainty factor. The Agency solicited feedback from the SAP on the utility of the PON1 data, by itself, for use in risk assessment; the SAP was similarly not supportive of using such data in isolation. Specifically, the SAP report states:

> *"...the information on PON1 polymorphisms should not be used as the sole factor in a data-derived uncertainty factor for two main reasons: 1) it is only one enzyme in a complex pathway, and is subsequent to the bioactivation reaction; therefore it can only function on the amount of bioactivation product (i.e., chlorpyrifos-oxon) that is delivered to it by CYP450); and 2) the genotype of PON1 alone is insufficient to predict vulnerability because the overall level of enzyme activity is ultimately what determines detoxification potential from that pathway; thus, it is better to use PON1 status because it provides information regarding PON1 genotype and activity. Some of the data from laboratory animal studies in PON knockout animals are using an unrealistic animal model and frequently very high dose levels, and do not reflect what might happen in humans."* (Ref. 7)

Based on a detailed review of the literature and the comments from the SAP, the Agency has determined that such data are not appropriate for use alone in deriving an intra-species uncertainty factor for use in human health risk assessment. As indicated by the SAP report, multiple factors (e.g., other enzymes such as P450s, carboxylesterases, butyrylcholinesterase) are likely to impact potential population sensitivity, rendering the results of the PON1 data, by themselves, insufficiently reliable to support a regulatory

conclusion about the potential variation of human sensitivity to chlorpyrifos.

Since the 2008 SAP, several epidemiological studies have been published that considered the association between PON status/genotype and health outcome. Hofmann et al. (2009) recently reported associations between PON1 status and inhibition of butyrylcholinesterase (BuChE) in a group of pesticide handlers in Washington. The authors note that this study requires replication with larger sample size(s) and more blood samples. (Ref. 8) Given the limitations of Hofmann et al., the Agency has not drawn any conclusions from this study. The Q/R-192 and/or C/T -108 polymorphism at the promoter site have been evaluated recently as a factor affecting birth or neurobehavioral outcomes following gestational exposure to OPs. (Refs. 9, 10, 11) These studies (Eskanazi., et al., 2010 (Ref. 9); Harley et al., 2011 (Ref. 10); Engel et al., 2011 (Ref. 11)) were evaluated by EPA in preparation for the April 2012 SAP review.

Petitioners further emphasize that the Furlong et al. study supports an intra-species uncertainty factor of over 164X given the range of variability seen in that study. The 164X value is derived from sensitivity observed in transgenic mice expressing human PON1Q-192 compared with mice expressing human PON1R-192 combined with the range of plasma arylesterase (AREase) from the newborn with the lowest PON1 level compared with the mother with the highest PON1 level from a group of 130 maternal-newborn pairs from the CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas) cohort.

EPA believes it is fundamentally at odds with international risk assessment practices to combine values from both mouse and human data to determine the potential

range of variability within a single species – regardless of whether the test animals express a human PON1 enzyme. As the 2008 FIFRA SAP explained, PON1 is but a single enzyme that should not be considered in isolation to predict the overall level of enzyme activity that may affect human sensitivity to a substance. Using a 164X intra-species uncertainty factor derived from the Furlong et al. study would take this practice one step further by relying upon combined PON1 values from different species with differing overall metabolic activity to derive the intra-species factor. EPA does not believe this approach is an appropriate means of determining the potential range of intra-species variability.

Finally, petitioners' assertion that the Furlong study supports an intra-species uncertainty factor of at least 150X is based on an analysis of that study that is inconsistent with EPA policy and widely- accepted international guidance on the development of intra-species uncertainty factors. In deriving the intra-species uncertainty factor in its risk assessments, EPA is guided by the principles of the 2005 IPCS (Ref. 12) guidance on chemical specific adjustment factors (CSAFs) and the EPA's 2014 Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation. (Ref. 13) These guidances recommend that intra-species factors should be extrapolated from a measure of central tendency in the population to a measure in the sensitive population (i.e., to extrapolate from a typical human to a sensitive human). To base the factor on the difference between the single lowest and highest measurements in a given study, as petitioners suggest in this instance, would likely greatly exaggerate potential intra-species variability. That approach effectively assumes that the point of departure in an EPA risk assessment will be derived

from the least sensitive test subject, thereby necessitating the application of an intra-species factor that accounts for the full range of sensitivity across a species. Since EPA does not develop its PoDs in this fashion; the approach suggested by petitioners is not appropriate.

In summary, the Agency has carefully considered the issue of PON1 variability and determined that data addressing PON1 in isolation are not appropriate for use alone in deriving an intra-species uncertainty factor and that the issue is more appropriately handled using a PBPK model. Further, the derivation of the 164X value advocated by the petitioners is based on combining values from humanized mice with human measured values with a range from highest to lowest; the Furlong et al. derivation is inappropriate and inconsistent with international risk assessment practice. (Ref. 2) The 2008 FIFRA SAP did not support the PON1 data used in isolation. Finally, petitioners' statement that the Furlong et al. study supports an intra-species uncertainty factor of at least 150X likely overstates potential variability. EPA therefore denies this aspect of the Petition.

2. *Endocrine Disrupting Effects*

a. Petitioners' claim. Petitioners summarize a number of studies evaluating the effects of chlorpyrifos on the endocrine system, asserting that, taken together, the studies "suggest that chlorpyrifos may be an endocrine disrupting chemical, capable of interfering with multiple hormones controlling reproduction and neurodevelopment." The petitioners then assert that EPA should not have delayed consideration of endocrine effects absent finalization of the Endocrine Disruptor Screening Program (EDSP) (Ref. 14) and should have quantitatively incorporated the studies into the chlorpyrifos IRED.

b. Agency Response. This portion of the Petition appears largely to be a complaint

about the completeness of EPA's reregistration decision and a request that EPA undertake quantitative incorporation of endocrine endpoints into its assessment of chlorpyrifos. The Petition does not explain whether and how endocrine effects should form the basis of a decision to revoke tolerances. The basis for seeking revocation of a tolerance is a showing that the pesticide is not "safe." Petitioners have neither asserted that EPA should revoke tolerances because effects on the endocrine system render the tolerances unsafe, nor have petitioners submitted a factual analysis demonstrating that aggregate exposure to chlorpyrifos presents an unsafe risk to humans based on effects on the endocrine system. Rather, the Petition appears to collect a number of studies suggesting that chlorpyrifos may have effects on the endocrine system and that EPA should have considered those health impacts at reregistration in a quantitative assessment.

To the extent that petitioners are seeking tolerance revocation on these grounds, the Petition fails to provide a sufficient basis for revocation because, in addition to the preceding defects, the cited data do not provide quantitative data (i.e. endpoints/points of departure) that indicate endocrine effects at doses that are more sensitive than the points of departure used in the chlorpyrifos risk assessment that are based on cholinesterase inhibition. While the cited studies provide qualitative information that exposure to chlorpyrifos may be associated with effects on the androgen and thyroid hormonal pathways, these data alone do not demonstrate that current human exposures from existing tolerances are unsafe. The Agency noted similar effects during its evaluation of information submitted by People for the Ethical Treatment of Animals (PETA) and the Physicians Committee for Responsible Medicine (PCRM) during its review of existing information as part of EPA's EDSP, as discussed below. Based on the review of that

data, EPA concluded that the effects seen in those studies do not call into question EPA's prior safety determinations supporting the existing tolerances; the data do not indicate a risk warranting regulatory action, and the petitioners have provided no specific information to alter this determination.

Consequently, the Petition does not support a conclusion that existing tolerances are unsafe due to potential endocrine effects. This portion of the Petition is therefore denied.

As petitioners may be aware, since the filing of the petition, EPA has completed the evaluation of chlorpyrifos under EPA's EDSP, as required under FFDCA section 408(p) that confirms EPA's conclusions. On April 15, 2009, a **Federal Register** notice was published in which chlorpyrifos was included in the initial list of chemicals (List 1) to receive EDSP Tier 1 test orders. The EDSP program is a two-tiered screening and testing program, Tier 1 and Tier 2 tests. Tier 1 includes 11 assays in the battery; these data are intended to allow EPA to determine whether certain substances (including pesticide active and other ingredients) have the potential to interact with the endocrine system and cause an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The purpose of Tier 2 tests is to identify and establish a quantitative, dose-response relationship for any adverse effects that might result from the interactions with the endocrine system.

On November 5, 2009, EPA issued Tier 1 test orders to the registrants of chlorpyrifos, requiring a battery of 11 screening assays to identify the potential to interact with the estrogen, androgen, or thyroid hormonal systems. (Ref. 15)

The agency received and reviewed all 11 EDSP Tier 1 screening assays for chlorpyrifos. On June 29, 2015, the agency completed the EDSP weight of evidence (WoE) conclusions for the Tier 1 screening assays for List 1 chemicals, including chlorpyrifos. In addition to the Tier 1 data, the WoE evaluations considered other scientifically relevant information (OSRI), including general toxicity data and open literature studies of sufficient quality. In determining whether chlorpyrifos interacts with the estrogen, androgen or thyroid pathways, the agency considered the number and type of effects induced, the magnitude and pattern of responses observed across studies, taxa, and sexes. Additionally, the agency also considered the conditions under which effects occurred, in particular whether or not endocrine-related responses occurred at dose(s) that also resulted in general systemic or overt toxicity. The agency concluded that, based on weight of evidence considerations, EDSP Tier 2 testing is not recommended for chlorpyrifos since there was no evidence of potential interaction with the estrogen, androgen and thyroid pathways. The EDSP Tier 1 WoE assessment and associated data evaluation records for chlorpyrifos are available online. (Ref. 16) This assessment further supports EPA's denial of this portion of the Petition.

3. Cancer Risks

a. Petitioners' claim. Petitioners claim that the Agency "ignored" a December 2004 National Institutes of Health Agricultural Health Study (AHS) by Lee et al. (2004) (Ref. 17) that evaluated the association between chlorpyrifos and lung cancer incidence. (Ref. 17) The petition summarizes the results of the AHS study, stating that the incidence of lung cancer has a statistically significant association with chlorpyrifos exposure. The Petition then asserts that these data are highly relevant and therefore should have been

referenced in the final aggregate assessment for chlorpyrifos or the OP CRA. Petitioners do not otherwise explain whether and how these data support the revocation of tolerances or the cancellation of pesticide registrations.

b. Agency Response. As explained in the previous section, the basis for seeking revocation of a tolerance is a showing that the pesticide is not "safe." Claiming that EPA failed to reference certain data in its risk assessment regarding carcinogenicity does not amount to illustrating that the tolerances are unsafe. To show a lack of safety, petitioners would have to present some fact-based argument demonstrating that aggregate exposure to chlorpyrifos poses an unsafe carcinogenic risk. Petitioners have not presented such an analysis. Accordingly, EPA is denying the Petition to revoke chlorpyrifos tolerances or cancel chlorpyrifos registrations to the extent the Petition relies on claims pertaining to carcinogenicity.

Despite the inadequacy of petitioners' cancer claims, in the course of the Agency's review of chlorpyrifos, EPA has examined the Lee et al. study cited by petitioners (Ref. 17) among other lines of evidence. EPA has concluded that the Lee et al. investigation does not alter the Agency's weight of evidence determination concerning chlorpyrifos' carcinogenic potential, and therefore does not alter the Agency's current cancer classification for chlorpyrifos. Specifically, the Agency does not believe this evidence raises sufficient grounds for concern regarding chlorpyrifos that EPA should consider initiating action based upon this information that might lead to revocation of the chlorpyrifos tolerances or cancellation of the chlorpyrifos registrations.

The Agency was aware of the December 2004 study cited by petitioners. While Lee et al. observed a possible association between chlorpyrifos use and the incidence of

lung cancer, the authors also stressed that further evaluation was necessary before concluding the association was causal in nature.(Ref. 17) Additional evaluation is necessary because of possible alternative explanations for the Lee et al. study, which include unmeasured confounding factors or confounding factors not fully accounted for in the analysis, and possible false positive results due to the performance of multiple statistical tests.

EPA has been a collaborating agency with the AHS since 1993, and continues to closely monitor the AHS literature. The Agency is working closely with the AHS researchers to clearly understand the results of their research efforts to ensure the Agency appropriately interprets these data as future studies are published. Between 2003 and 2009 there have been six nested case-control analyses within the AHS which evaluated the use of a number of agricultural pesticides, including chlorpyrifos, in association with specific anatomical cancer sites, in addition to the previously published cohort study (Ref. 17) cited by the petitioners. As noted below, both the Agency and Health Canada have comprehensively reviewed these data.

In accordance with the Agency's 2005 Guideline for Cancer Risk Assessment (Ref. 18), chlorpyrifos is classified as "Not Likely to be Carcinogenic to Humans" based on the lack of evidence of carcinogenicity in male or female mice and male or female rats. In chronic toxicity/ carcinogenicity studies, animals received chlorpyrifos in their feed every day of their lives (78 weeks for mice and 104 weeks for rats) at doses thousands of times greater than any anticipated exposure to humans from authorized uses. There was no evidence of cancer in the experimental animal studies. Additionally, available evidence from *in vivo* and *in vitro* assays did not support a mutagenic or

genotoxic potential of chlorpyrifos.

Recently, the Agency conducted its own review of the six nested case-control analyses and one cohort study within the AHS concerning the carcinogenic potential of chlorpyrifos. (Ref. 19) EPA concluded with respect to the AHS lung cancer results that the findings are useful for generating hypotheses, but require confirmation in future studies. This conclusion is consistent with that of researchers from Health Canada. Specifically, Weichenthal et al. (2010) (Ref. 20) published a review article in Environmental Health Perspectives on pesticide exposure and cancer incidence in the AHS cohort. Their review of these same studies concluded that the weight of experimental toxicological evidence does not suggest that chlorpyrifos is carcinogenic, and that epidemiologic results currently available from the AHS are inconsistent, lack replication, and lack a coherent biologically plausible carcinogenic mode of action. The authors did note positive exposure-response associations for chlorpyrifos and lung cancer in two separate evaluations.

In summary, while there is initial suggestive epidemiological evidence of an association between chlorpyrifos and lung cancer to only form a hypothesis as to a carcinogenic mode of action, additional research (including follow-up AHS research) is needed to test the hypothesis. Consequently, at this time it is reasonable to conclude chlorpyrifos is not a carcinogen in view of the lack of carcinogenicity in the rodent bioassays and the lack of a genotoxic or mutagenic potential. The Agency concludes that existing epidemiological data (including Lee et al.) do not change the current weight of the evidence conclusions. The Agency continues to believe there is not a sufficient basis to alter its assessment of chlorpyrifos as not likely to be carcinogenic to humans when

multiple lines of evidence are considered (e.g., epidemiology findings, rodent bioassay, genotoxicity); therefore, chlorpyrifos cancer risk would not be a factor in any potential Agency risk determination to revoke tolerances for chlorpyrifos.

4. CRA misrepresents risks, failed to apply FQPA10X Safety Factor

a. Petitioners' claim. Petitioners assert that EPA relied on limited data and inaccurate interpretations of data to support its decision to remove the FQPA safety factor in the 2006 OP CRA. Specifically, the petitioners challenge the Agency's use of data from a paper by Zheng et al. (2000) (Ref. 21) claiming that, in contrast to the Agency's analysis of the study data, the data does show an obvious difference between juvenile and adult responses to chlorpyrifos. Petitioners conclude by asserting that the Zheng et al. study supports using a 10X safety factor for chlorpyrifos in the CRA.

b. Agency Response. Petitioners' assertions do not provide a sufficient basis for revoking chlorpyrifos tolerances. As explained previously, the ground for seeking revocation of a tolerance is a showing that the pesticide is not "safe." The petitioners' claim that the data EPA relied upon support a different FQPA safety factor for chlorpyrifos in the CRA does not amount to a showing that chlorpyrifos tolerances are unsafe. To show a lack of safety, petitioners would have to present a factual analysis demonstrating that the lack of a 10X safety factor in the CRA for chlorpyrifos poses unsafe cumulative exposures to the OPs. Petitioners have not made such a showing. For this reason, EPA is denying the petitioners' request to revoke chlorpyrifos tolerances or cancel chlorpyrifos registrations to the extent that request relies on claims pertaining to EPA's failure to provide a 10X safety factor in the 2006 CRA based on the results of the Zheng et al. study.

Despite the inadequacy of petitioners' FQPA safety factor claims, EPA examined the evidence cited by petitioners for the purpose of evaluating whether the evidence raises sufficient grounds for concern regarding chlorpyrifos that EPA should consider initiating the actions sought by the petitioners.

In general, when the Agency conducts a cumulative assessment, the scope of cumulative risk is limited to the common mechanism endpoint -- which in this case of the 2006 OP CRA, was cholinesterase inhibition, the primary toxicity mode of action for the OPs. As such, for the OP CRA, experimental toxicology data on AChE inhibition were used for developing relative potency estimates, points of departure, and informing the FQPA safety factor used in the OP CRA. EPA relied on brain AChE data from adult female rats dosed for 21 days or longer for estimating relative potency and points of departure. At approximately three weeks of oral exposure to OPs, AChE inhibition reaches steady state in the adult rat such that continued dosing does not result in increased inhibition. This timeframe of toxicity (21-days and longer) was selected as there was high confidence in the potency estimates derived from the steady state toxicology studies due to the stability of the AChE inhibition.

The Agency's 2006 OP CRA contained EPA's complete FQPA safety factor analysis, (Ref. 22) which involved consideration of pre-natal and post-natal experimental toxicology studies, in addition to exposure information. In the OP CRA, pre-natal exposure AChE studies in rats show that the fetus is no more sensitive than the dam to AChE inhibition and the fetus is often less sensitive than the dam. Thus, evaluating the potential for increased toxicity of juveniles from post-natal exposure was a key

component in determining the magnitude of the FQPA safety factors in the OP CRA. Furthermore, because characteristics of children are directly accounted for in the cumulative exposure assessment, the Agency's methods did not underestimate exposure to OPs.

In the 2006 OP CRA, each OP was assigned a 10X FQPA safety factor unless chemical-specific AChE data on young animals were available to generate a data derived safety factor. To best match the relative potency factor (RPF)s and PODs based on repeated dosing, the Agency used repeated dosing data in juveniles for developing the FQPA safety factors. For chlorpyrifos, at the time of the 2006 OP CRA, the only such data available were from the Zheng et al. literature study.

The petitioners are correct that Dr. Carey Pope of Oklahoma State University provided the Agency with the raw data from the Zheng et al. study. These raw data were used to develop the plot in the 2006 OP CRA which was reproduced in the Petition. Petitioners accurately note that for other OPs a benchmark dose modeling approach was used and that no BMD values were reported for chlorpyrifos. In determining the FQPA safety factor, petitioners claim that the Agency misinterpreted the brain AChE data from Zheng et al.

As shown in the plot reproduced on page 15 of the Petition, the dose-response data in the Zheng et al. study are variable and lack a monotonic shape at the low dose end of the dose response curve. The Agency acknowledges that at the high dose, the pups appear to be more sensitive. However, at the low dose end of the response curve, relevant for human exposures and, thus, the cumulative risk assessment (i.e., at or near the 10% inhibition level), little to no difference is observed. Therefore, despite the lack

of BMD estimates for the Zheng et al. study, the Agency is confident in the value used to address the common mechanism endpoint (AChE inhibition) addressed in the 2006 CRA. Since that time, the Agency attempted BMD modeling of the Zheng et al. data as part of the 2011 preliminary chlorpyrifos HHRA (Ref. 23) which yielded low confidence results due to the variability in the data.

Dow AgroSciences submitted a comparative cholinesterase study (CCA) for chlorpyrifos. CCA studies are specially designed studies to compare the dose-response relationship in juvenile and adult rats. This CCA study includes two components: 1) acute, single dosing in post-natal day 11 and young adult rats and 2) 11-days of repeating dosing in rat pups from PND11-21 and 11-days of repeated dosing in adult rats. The CCA study for chlorpyrifos is considered by EPA to be high quality and well-designed. The preliminary risk assessment for chlorpyrifos' reports BMD estimates from this CCA study. Specifically, for the repeated dosing portion of the study, the BMD_{10s} of 0.80 (0.69 $BMDL_{10}$) and 1.0 (0.95 $BMDL_{10}$) mg/kg/day respectively for female pups and adults support the FQPA safety factor of 1X for the AChE inhibition endpoint used in the 2006 OP CRA. As such, petitioners' claims regarding the CRA and FQPA safety factor is denied.

5. Over-reliance on registrant data.

a. Petitioners' claims. Petitioners assert that in reregistering chlorpyrifos EPA "cherry picked" data, "ignoring robust, peer-reviewed data in favor of weak, industry-sponsored data to determine that chlorpyrifos could be re-registered and food tolerances be retained." As such, the Agency's reassessment decision is not scientifically defensible.

b. Agency response. This portion of the Petition does not purport to be an independent basis for revoking chlorpyrifos tolerances or cancelling chlorpyrifos registrations. Rather, this claim appears to underlie petitioners' arguments in other sections of the Petition. While petitioners claim that EPA ignored robust, peer-reviewed data in favor of weak, industry-sponsored data for the reregistration of chlorpyrifos, petitioners do not cite to any studies other than those used to support their other claims. In general, petitioners did not provide any studies in the Petition that EPA failed to evaluate. Since the specific studies cited by petitioners are not associated with this claim, but rather their other claims, EPA's response to the specific studies are, therefore, addressed in its responses to petitioners' other claims. However, EPA explains below why, as a general matter, the Agency does not believe it "over-relied" on registrant data in evaluating the risks of chlorpyrifos in its 2006 reregistration decision.

In spite of petitioners' claim, the Agency does not ignore robust, peer-reviewed data in favor of industry-sponsored data. Further, EPA has a very public and well-documented set of procedures that it applies to the use and significance accorded all data utilized to inform risk management decisions. Registrant generated data, in response to FIFRA and FFDCA requirements, are conducted and evaluated in accordance with a series of internationally harmonized and scientifically peer-reviewed study protocols designed to maintain a high standard of scientific quality and reproducibility. (Refs. 23 and 24).

Additionally, to further inform the Agency's risk assessment, EPA is committed to the consideration of other sources of information such as data identified in the open, peer-reviewed literature and information submitted by the public as part of the regulatory

evaluation of a pesticide. An important issue, when evaluating any study, is its scientific soundness and quality, and thus, the level of confidence in the study findings to contribute to the risk assessment.

The literature was searched, fully considered, and provided additional information on, chlorpyrifos mode of action, pharmacokinetics, epidemiology, neurobehavioral effects in laboratory animals, and age dependent sensitivity to cholinesterase inhibition.

Therefore, by evaluating registrant data in accordance with internationally harmonized and scientifically peer-reviewed study protocols, undertaking thorough open literature searches, and considering information provided by the public, the Agency is confident that its assessment for chlorpyrifos in 2006 was reasonably based upon the best available science at the time of the assessment. Previous sections of this response to petitioners' claims regarding the Agency's inadequate use of various data only further highlights and supports the scientifically defensible results of the Agency's assessment. Petitioners' claim that the Agency overly relies on registrant data is therefore denied.

6. EPA has failed to properly address the exporting hazard in foreign countries from chlorpyrifos.

As noted in Unit II., in EPA's July 16, 2012 interim petition response EPA issued a final denial of this claim. That denial constituted final agency action and EPA is not reopening consideration of that claim.

7.-9. EPA failed to quantitatively incorporate data demonstrating long-lasting effects from early life exposure to chlorpyrifos in children; EPA disregarded data demonstrating that there is no evidence of a safe level of exposure during pre-birth and early life stages; EPA failed to cite or quantitatively incorporate studies and clinical

reports suggesting potential adverse effects below 10% cholinesterase inhibition.

a. *Petitioners' claims.* The petitioners assert that human epidemiology and rodent developmental neurotoxicity data suggest that pre-natal and early life exposure to chlorpyrifos can result in long-lasting, possibly permanent damage to the nervous system and that these effects are likely occurring at exposure levels below 10% cholinesterase inhibition, EPA's existing regulatory standard for chlorpyrifos and other OPs. They assert that EPA has therefore used the wrong endpoint as a basis for regulation and that, taking into account the full spectrum of toxicity, chlorpyrifos does not meet the FFDCA safety standard or the FIFRA standard for registration.

b. Agency response. EPA has grouped claims 7-9 together because they fundamentally all raise the same issue: whether the potential exists for chlorpyrifos to cause neurodevelopmental effects in infants and children from exposures (either to mothers during pregnancy or directly to infants and children) that are lower than those resulting in 10% cholinesterase inhibition – the basis for EPA's long-standing point of departure in regulating chlorpyrifos and other OPs. While petitioners may perhaps disagree, unlike the claims addressed above, these claims were not truly challenges to EPA's 2006 reregistration decision for chlorpyrifos, but rather, challenges to EPA's ongoing approval of chlorpyrifos under FIFRA and the FFDCA that rely in large measure on data published after EPA completed both its 2001 chlorpyrifos Interim Reregistration Decision and the 2006 OP CRA that concluded the reregistration process for chlorpyrifos and all other OPs. As matters that largely came to light after the completion of reregistration, these petition issues are issues to be addressed as part of the registration review of chlorpyrifos – the next round of re-evaluation under section 3(g) of FIFRA. As

petitioners are aware, past EPA administrations prioritized the registration review of the OPs in no small measure to begin to focus on the question of OP neurodevelopmental toxicity, which was, and remains, an issue at the cutting edge of science, involving significant uncertainties. EPA has three times presented approaches and proposals to the FIFRA SAP for evaluating recent epidemiologic data (some of which is cited in the Petition) exploring the possible connection between *in utero* and early childhood exposure to chlorpyrifos and adverse neurodevelopmental effects. The SAP's reports have rendered numerous recommendations for additional study and sometimes conflicting advice for how EPA should consider (or not consider) the epidemiology data in conducting EPA's registration review human health risk assessment for chlorpyrifos. While industry and public interest groups on both sides of this issue can debate what the recommendations mean and which recommendations should be followed, one thing should be clear to all persons following this issue: the science on this question is not resolved and would likely benefit from additional inquiry.

EPA has, however, been unable to persuade the 9th Circuit Court of Appeals that further inquiry into this area of unsettled science should delay EPA's response to the Petition. Faced with an order requiring EPA to respond to the Petition, in October 2015, EPA chose to issue a proposed rule to revoke all chlorpyrifos tolerances based in part on the uncertain science surrounding neurodevelopmental toxicity suggested by certain epidemiology studies. The comments EPA has received on that proposal and on EPA's November 17, 2016 NODA suggest that there continue to be considerable areas of uncertainty with regard to what the epidemiology data show and deep disagreement over how those data should be considered in EPA's risk assessment.

Although not a legal consideration, it is important to recognize that for many decades chlorpyrifos has been and remains one of the most widely used pesticides in the United States, making any decision to retain or remove this pesticide from the market an extremely significant policy choice. In light of the significance of this decision and in light of the significant uncertainty that exists regarding the potential for chlorpyrifos to cause adverse neurodevelopmental effects, EPA's preference is to fully explore approaches raised by the SAP and commenters on the proposed rule, and possibly seek additional authoritative peer review of EPA's risk assessment prior to finalizing any regulatory action in the course of registration review. As the 9th Circuit has made clear in its August 12, 2016 order in *PANNA v. EPA*, EPA must provide a final response to the Petition by March 31, 2017, regardless of whether the science remains unsettled and irrespective of whatever options may exist for more a complete resolution of these issues during the registration review process.

While EPA acknowledges its obligation to respond to the Petition as required by the court, the court's order does not and cannot compel EPA to complete the registration review of chlorpyrifos in advance of the October 1, 2022 deadline provided in section 3(g) of FIFRA, 7 U.S.C. 136a(g). Although past EPA administrations had chosen to attempt to complete that review several years in advance of the statutory deadline (and respond to the Petition on the same time frame), it has turned out that it is not possible to fully address these issues early in the registration review period. As a result, EPA has concluded that it should alter its priorities and adjust the schedule for chlorpyrifos so that it can complete its review of the science addressing neurodevelopmental effects prior to making a final registration review decision whether to retain, limit or remove

chlorpyrifos from the market. Accordingly, EPA is denying these Petition claims and intends to complete a full and appropriate review of the neurodevelopmental data before either finalizing the proposed rule of October 30, 2015, or taking an alternative regulatory path.

EPA's denial of the Petition on the grounds provided above is wholly consistent with governing law. The petition provision in FFDCA section 408(d) does not address the timing for responding to this petition nor does it limit the extent to which EPA may coordinate its petition responses with the registration review provisions of FIFRA section 3(g). Further, provided EPA completes registration review by October 1, 2022, Congress otherwise gave the EPA Administrator the discretion to determine the schedule and timing for completing the review of the approximately over 1000 pesticide active ingredients currently subject to evaluation under section 3(g). EPA may lawfully re-prioritize the registration review schedule developed by earlier administrations provided that decision is consistent with law and an appropriate exercise of discretion. *See Federal Communications Commission v. Fox Television Stations*, 129 S.Ct. 1800 (2009) (Administrative Procedure Act does not require that a policy change be justified by reasons more substantial than those required to adopt a policy in the first instance). Nothing in FIFRA section 3(g) precludes EPA from altering a previously established registration review schedule. Given the absence of a clear statutory directive, FIFRA and the FFDCA provide EPA with discretion to take into account EPA's registration review of a pesticide in determining how and when the Agency responds to FFDCA petitions to revoke tolerances. As outlined above, given the importance of this matter and the fact that critical questions remain regarding the significance of the data

addressing neurodevelopmental effects, EPA believes there is good reason to extend the registration review of chlorpyrifos and therefore to deny the Petition. To find otherwise would effectively give petitioners under the FFDCA the authority to re-order scheduling decisions regarding the FIFRA registration review process that Congress has vested in the Administrator.

10. Inhalation Exposure from Volatilization

a. Petitioners' claim. Petitioners assert that when EPA completed its 2006 OP CRA, EPA failed to consider and incorporate significant exposures to chlorpyrifos-contaminated air that exist for some populations in communities where chlorpyrifos is applied. Petitioners assert that these exposures exceeded safe levels when considering cholinesterase inhibition as a point of departure and that developmental neurotoxicity may occur at even lower exposure levels than those resulting in cholinesterase inhibition.

b. Agency response. To the extent petitioners are asserting that human exposure to chlorpyrifos spray drift and volatilized chlorpyrifos present neurodevelopmental risks for infants and children, EPA is denying this claim for the reasons stated above in our response to claims 7-9. As noted, EPA believes that, given the uncertainties associated with this identified risk concern, the appropriate course of action is for EPA to deny the Petition and work to further resolve this area of unsettled science in the time remaining for the completion of registration review under section 3(g) of FIFRA.

With respect to petitioners' claim that exposures to spray drift and volatilized chlorpyrifos present a risk from cholinesterase inhibition, EPA is denying the Petition for the reasons previously identified in EPA's Spray Drift Mitigation Decision of July 16, 2012 [EPA-HQ-OPP-2008-0850] and EPA's interim response of July 15, 2014 [EPA-

HQ-OPP-2007-1005] addressing chlorpyrifos volatilization. In the Spray Drift Mitigation Decision, EPA determined that the chlorpyrifos registrants' adoption of label mitigation (in the form of label use rate reductions and no spray buffer zones) eliminated risk from cholinesterase inhibition as a result of spray drift. As for risks presented by volatilized chlorpyrifos that may occur following application, EPA's July 15, 2014 interim response to the Petition explained that recent vapor phase inhalation studies for both chlorpyrifos and chlorpyrifos-oxon made clear that neither vapor phase chlorpyrifos nor chlorpyrifos-oxon presents a risk of cholinesterase inhibition. Specifically, those studies, as indicated in EPA's memorandum, *Chlorpyrifos: Reevaluation of the Potential Risks from Volatilization in Consideration of Chlorpyrifos Parent and Oxon Vapor Inhalation Toxicity Studies* (Ref. 25), revealed that levels of chlorpyrifos and chlorpyrifos-oxon in vapor form are much lower than the levels seen in earlier aerosol studies that are better suited for evaluating spray drift. Indeed, no cholinesterase inhibition was observed in either volatility study. What is clear from these data is that the air cannot hold levels of volatilized chlorpyrifos or its oxon that are capable of causing adverse effects from cholinesterase inhibition.

VI. Regulatory Assessment Requirements

As indicated previously, this action announces the Agency's order denying a petition filed, in part, under section 408(d) of FFDCA. As such, this action is an adjudication and not a rule. The regulatory assessment requirements applicable to rulemaking do not, therefore, apply to this action.

VII. Submission to Congress and the Comptroller General

The Congressional Review Act, 5 U.S.C. 801 *et seq*., does not apply because this

action is not a rule for purposes of 5 U.S.C. 804(3).

IX. References

The following is a listing of the documents that are specifically referenced in this document. The docket includes these documents and other information considered by EPA, including documents that are referenced within the documents that are included in the docket, even if the referenced document is not physically located in the docket. For assistance in locating these other documents, please consult the technical person listed under FOR FURTHER INFORMATION CONTACT.

1. The Petition from NRDC and PANNA and EPA's various responses to it are available in docket number EPA-HQ-OPP-2007-1005 available at *http://www.regulations.gov.*

2. FIFRA Scientific Advisory Panel (2016). "Chlorpyrifos: Analysis of Biomonitoring Data". Available at: *https://www.epa.gov/sap/meeting-materials-april-19-21-2016-scientific-advisory-panel.*

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5. U.S. EPA (2008). Draft Appendix E available at *http://www.epa.gov/scipoly/sap/meetings/2008/september/appendixe.pdf*. Draft Science Issue Paper: Chlorpyrifos Hazard and Dose Response Characterization. August 21, 2008.

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7. U.S. EPA (2008). Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held September 16-18, 2008 on the Agency's Evaluation of the Toxicity Profile of Chlorpyrifos. Available at *http://www.epa.gov/scipoly/sap/meetings/2008/september/sap0908report.pdf* at 61.

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9. Hofmann, J.N., Keifer, M.C., Furlong, C.E., De Roos, A.J., Farin., F.M., Fenske, R.A., van Belle, G., Checkoway, H. (2009) Serum Cholinesterase Inhibition in Relation to Paraoxonase-1 (PON1) Status among Organophosphate-Exposed Agricultural Pesticide Handlers./ Environ Health Perspect 117:1402–1408 (2009). doi:10.1289/ehp.0900682. Available at http://dx.doi.org/ [Online 9 June 2009].

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Study Exposed to Organophosphate Pesticides in Utero. Environmental Health Perspectives. Vol 118 (12): 1775-1781).

11. Harley KG, Huen K, Schall RA, Holland NT, Bradman A, et al. (2011) Association of Organophosphate Pesticide Exposure and Paraoxonase with Birth Outcome in Mexican-American Women. PLoS ONE 6(8): e23923. doi:10.1371/journal.pone.0023923.

12. IPCS (International Programme on Chemical Safety) 2005. Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/Concentration-Response Assessment. Harmonization Project Document No. 2. World Health Organization, International Programme on Chemical Safety, Geneva, Switzerland.

13. U.S. EPA (2014). Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation. Available at *https://www.epa.gov/risk/guidance-applying-quantitative-data-develop-data-derived-extrapolation-factors-interspecies-and.*

14. For additional information on the Endocrine Disruptor Screening program see *http://www.epa.gov/endo/.*

15. For information related to the status of EDSP test orders/DCIs, status of EDSP OSRI: order recipient submissions and EPA responses, and other EDSP assay information see http://www.epa.gov/endo/pubs/toresources/index.htm.

16. For available Data Evaluation Records (DERs) for EDSP Tier 1, see https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-tier-1-

screening-determinations-and.

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22. For additional information on the organophosphate cumulative risk assessment, see *http://epa.gov/pesticides/cumulative/2006-op/op_cra_main.pdf.*

23. U.S. EPA (2011). Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration. Available in docket number EPA-HQ-OPP-2008-0850, http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0025.

(23) For additional information on EPA's Harmonized Test Guidelines and

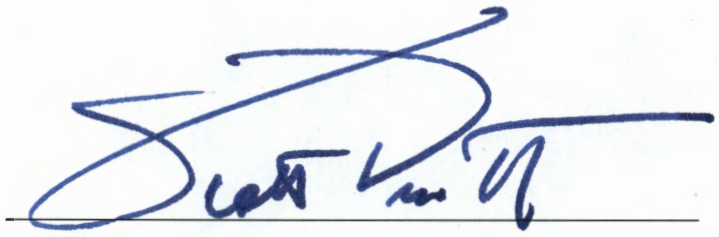
international efforts at harmonization, see

http://www.epa.gov/opp00001/science/guidelines.htm.

(24) Available at http://*www.regulations.gov* in docket EPA-HQ-OPP-2008-0850.

Authority: 7 U.S.C. 136 *et seq.* and 21 U.S.C. 346a.

Dated: 3/29/2017.



E. Scott Pruitt,

Administrator.

DEPARTMENT OF AGRICULTURE AND MEASUREMENT STANDARDS

GLENN FANKHAUSER
Agricultural Commissioner
Sealer of Weights and Measures

1001 South Mount Vernon Avenue · Bakersfield, California 93307
Telephone 661-868-6300 · Fax 661-868-6301 · agcomm@kerncounty.com
website - www.kernag.com

PRESS RELEASE

August 8, 2017

Kern County Dept. of Ag. Fines Two Companies for Pesticide Drift Incident

BAKERSFIELD, August 8, 2017 –

The Kern County Department of Agriculture and Measurement Standards (KCDAMS) has taken swift enforcement action against two companies who violated pesticide rules and ordered them to pay a total of $50,250 after an incident left 5 people seeking medical treatment.

The two companies are Sun Pacific Farming – Maricopa, 33374 Lerdo Hwy, Bakersfield, CA and Grape Man Farms, LP, P.O. Box 1266 Delano, CA.

The enforcement action comes after KCDAMS carried out an investigation into an incident on May 5, 2017, when a crew of fieldworkers harvesting cabbage in a field in the area of Maricopa south of Copus Road and west of I-5 (Section 32, Township 12N Range 22W) complained of an odor.

Sun Pacific Farming – Maricopa had treated tangerine orchards located one-half mile west and northwest of the site with a pesticide product called Vulcan (active ingredient chlorpyrifos) which was just being completed as the cabbage harvesters were arriving. Grape Man Farms, LP had treated vineyards located one-half mile northwest of the cabbage site with Cosavet DF (active ingredient sulfur) during the time the incident occurred.

As part of the investigation, KCDAMS submitted foliage samples to a laboratory for analysis. The lab found the presence of sulfur and chlorpyrifos, indicating that both pesticides had drifted from where they were applied – a violation of California law. The KCDAMS investigation determined that the drift and illness occurred as a direct result of violating pesticide laws.

"Agriculture is vitally important to Kern County. At the same time, we want to do everything we can to protect the public and the environment. Integral to this is agricultural worker safety" said Glenn Fankhauser, Kern County Agricultural Commissioner.

During the May 5th incident the Kern County Fire Department was dispatched along with Kern County Environmental Health and inspectors from the KCDAMS. At one point, as many as 37 workers experienced symptoms; however, only five people sought medical treatment.

Sun Pacific Farming – Maricopa has been ordered to pay a civil penalty totaling $30,250 for violating California pesticide laws and/or regulations including:

- Not using the pesticide Vulcan according to the label directions
- Using the pesticide Vulcan in a manner that exposed five workers, causing illness

Grapeman Farms, LP has been ordered to pay a civil penalty totaling $20,000 for violating California pesticide laws and/or regulations including:

- Not using the pesticide Cosavet DF according to the label directions
- Using the pesticide Cosavet DF in a manner that exposed five workers, causing illness

Copies of the Notice of Proposed Actions (NOPAs) outlining the individual violations and fine levels is attached. Both entities have the opportunity to request a hearing related to these charges as well as an appeal of the hearing results if desired.

Further information can be obtained by calling the Kern County Department of Agriculture at 661-868-6300.

DEPARTMENT OF AGRICULTURE AND MEASUREMENT STANDARDS

GLENN FANKHAUSER
Agricultural Commissioner
Sealer of Weights and Measures

1001 South Mount Vernon Avenue · Bakersfield, California 93307
Telephone 661-868-6300 · Fax 661-868-6301 · agcomm@kerncounty.com
website – www.kernag.com

NOTICE OF PROPOSED ACTION, NATURE OF VIOLATION, AND RIGHT TO REQUEST HEARING

Sun Pacific Farming - Maricopa
33374 Lerdo Hwy
Bakersfield, CA 93308

Restricted Material Permit Number: 15-17-1504087
File Number: 010-ACP-KER-17/18

You are hereby notified that the Agricultural Commissioner for the County of Kern proposes that you be fined a total amount of $30,250.00 as a civil penalty for five (5) separate violations of California's pesticide law(s) and/or regulation(s) as explained below. The authority for this action is granted to the County Agricultural Commissioner pursuant to the provisions of Section 12999.5 of the California Food and Agricultural Code (FAC). Furthermore, enforcement and fine regulations are found in Title 3, California Code of Regulations (3 CCR), sections 6128, 6130 and 6131.

FACTUAL CIRCUMSTANCES OF VIOLATION AND FINE EXPLANATION

You are charged with violating California's pesticide law(s) and/or regulation(s) as cited below. A brief description of the nature of the violation, the facts of the violation, and how the fine level was determined follows:

On May 5, 2017, at 8:05 a.m., the Kern County Department of Agriculture and Measurement Standards (Department) received a telephone call from Dan Andrews of Dan Andrew Farms LLC (Restricted Materials Permit number 15-17-1502454), reporting workers harvesting his cabbage in site 57C, located in Section 32, Township 12N, Range 22W, complained of an odor. Shortly afterwards, our Department was contacted by Kern County Emergency Services that the Kern County Fire Department was responding to a crew of field workers harvesting in a cabbage field that were complaining of an odor making them sick that may involve pesticides. Our Department began a priority exposure investigation into this incident (34-KER-17). During this investigation, it was discovered that Sun Pacific Farming – Maricopa (Restricted Materials Permit number 15-17-1504087) made pesticide applications of Vulcan® (EPA Registration Number 66222-233) to their seedless tangerine sites 390I, 390J, 390K, 390L, 390M, 390N and 390Q beginning on May 4, 2017, at 6:00 p.m. through May 5, 2017, 6:25 a.m. On May 5, 2017, a crew of forty-eight people harvesting in Dan Andrews Farms LLC cabbage field (Site 57C) noticed an odor. Several of the crew members experienced symptoms and five of the crew members sought medical attention. The tangerine sites treated by Sun Pacific Farming-Maricopa are located 0.5 miles west of cabbage site 57C. Samples were taken by our Department and lab

analysis revealed a gradient drift pattern from tangerine site 390L to cabbage site 57C all testing positive for chlorpyrifos which is the active ingredient of Vulcan®.

The Kern County Department of Agriculture and Measurement Standards alleges that Sun Pacific Farming-Maricopa made applications of Vulcan® in conflict with the registered pesticide label in violation of California Food and Agricultural Code (FAC) Section 12973 and California Code of Regulations (CAC) Section 6600(b) which caused the incident stated above.

On May 11, 2017, a Pest Control Headquarters and Employee Safety Inspection number 109-15-17-M007-001 was conducted on Sun Pacific Farming-Maricopa. During the inspection, the following noncompliance was found: There was no record of a medical evaluation for the use of a respirator for three of the applicators – Manuel Rivera, Artemio Gonzales and Alfredo Garcia. Sun Pacific Farming – Maricopa violated California Code of Regulations Section 6739(d)(5)(A) by failing to ensure that medical evaluations were conducted on their employees before the employee was required to use a respirator.

VIOLATION I

Under FAC Section 12973 it is unlawful to use any pesticide in conflict with the pesticide's registered label. Vulcan® pesticide product labeling states "Apply only as a medium or coarser spray (ASABE standard 572.1) or a volume mean diameter of 300 microns or greater for spinning atomizer nozzles". Sun Pacific Farming-Maricopa violated FAC Section 12973 by applying the pesticide Vulcan® using nozzles from the TJTXR series that put out a fine spray. By using incorrect nozzles that put out a fine spray, Sun Pacific Farming-Maricopa failed to meet the volume mean diameter of 300 microns or greater requirement on the label and the label requirement to apply only as a medium or coarser spray. Sun Pacific Farming-Maricopa personnel admitted that they did not meet this labeling requirement during interview statements collected during our investigation.

PENALTY SUMMARY

The Agricultural Commissioner proposes to fine you $5,000.00 for the above described violation. The violation is considered a Class "A" violation. A Class "A" violation is a violation of a law or regulation that caused a health, property, or environmental hazard. Sun Pacific Farming-Maricopa caused a hazard to the health of workers, property, and the environment by applying Vulcan® in conflict with a label requirement intended to prevent drift of the product which resulted in drift of the product onto Dan Andrews Farms LLC cabbage site 57C leading five field workers to seek medical attention.

The fine range for a Class "A" violation is $700.00 to $5,000.00. This fine for a violation of Section 12973 of California Food and Agricultural Code was placed at the top of the fine range because it is a violation of a label requirement intended to prevent drift and therefore by not following this label requirement it created a health hazard leading five field workers to seek medical attention.

CODE SECTION VIOLATED

California Food and Agricultural Code Section 12973 states:

The use of any pesticide shall not conflict with labeling registered pursuant to this chapter which is delivered with the pesticide or with any additional limitations applicable to the conditions of any permit issued by the director or commissioner.

VIOLATION II

Under FAC Section 12973 it is unlawful to use any pesticide in conflict with the pesticide's registered label. Vulcan® pesticide product labeling states, "For airblast applications, turn off all outward pointing nozzles at row ends and when spraying the outer two rows". Sun Pacific violated FAC section 12973 by failing to turn off all outward pointing nozzles when spraying the outer two rows. Sun Pacific Farming-Maricopa's practice is to spray from the outside edge with only the nozzles facing inward turned on, or to spray one row in with all nozzles on which does not meet labeling requirement to turn off all outward pointing nozzles at row ends and when spraying the outer two rows.

PENALTY SUMMARY

The Agricultural Commissioner proposes to fine you $5,000.00 for the above described violation. The violation is considered a Class "A" violation. A Class "A" violation is a violation of a law or regulation that caused a health, property, or environmental hazard. Sun Pacific Farming-Maricopa caused a hazard to the health of workers, property, and the environment by applying Vulcan® in conflict with a label requirement intended to prevent drift of the product which resulted in drift of the product onto Dan Andrews Farms LLC cabbage site 57C leading five field workers to seek medical attention.

The fine range for a Class "A" violation is $700.00 to $5,000.00. This fine for a violation of FAC Section 12973 was placed at the top of the fine range because it is a violation of a label requirement intended to prevent drift and therefore by not following this label requirement it created a health hazard leading five field workers to seek medical attention.

CODE SECTION VIOLATED

California Food and Agricultural Code Section 12973 states:

The use of any pesticide shall not conflict with labeling registered pursuant to this chapter which is delivered with the pesticide or with any additional limitations applicable to the conditions of any permit issued by the director or commissioner.

VIOLATION III

Under FAC Section 12973 it is unlawful to use any pesticide in conflict with the pesticide's registered label. Vulcan® pesticide product labeling states, "Do not allow spray to drift from application site and contact people, structures people occupy at any time and the associated property, parks and recreation areas, nontarget crops, aquatic and wetland areas, woodlands, pastures, rangelands, or animals". Sun Pacific Farming-Maricopa violated FAC section 12973 by applying the pesticide Vulcan® by allowing the pesticide to drift onto nontarget crops. In this case, Sun Pacific Farming-Maricopa allowed the pesticide to drift off-site by making applications of Vulcan® with fine droplets using outward pointing nozzles along the edges of the fields.

PENALTY SUMMARY

The Agricultural Commissioner proposes to fine you $5,000.00 for the above described violation. The violation is considered a Class "A" violation. A Class "A" violation is a violation of a law or regulation that caused a health, property, or environmental hazard. Sun Pacific Farming-Maricopa caused a hazard to the health of workers, property, and the environment by applying Vulcan® in conflict with a label requirement intended to prevent drift of the product which resulted in drift of the product onto Dan Andrews Farms LLC cabbage site 57C leading five field workers to seek medical attention.

The fine range for a Class "A" violation is $700.00 to $5,000.00. This fine for a violation of FAC Section 12973 was placed at the top of the fine range because it is a violation of a label requirement intended to prevent drift and therefore by not following this label requirement it created a health hazard leading five field workers to seek medical attention.

CODE SECTION VIOLATED

California Food and Agricultural Code Section 12973 states:

The use of any pesticide shall not conflict with labeling registered pursuant to this chapter which is delivered with the pesticide or with any additional limitations applicable to the conditions of any permit issued by the director or commissioner.

VIOLATION IV

Sun Pacific Farming – Maricopa violated 3CCR Section 6600(b) by failing to perform all pest control in a careful and effective manner. The three previous Vulcan ® pesticide label violations of California Food and Agricultural Code Section 12973 above indicate that Sun Pacific did not perform all pest control in a careful and effective manner as required by the California Code of Regulations section 6600(b).

PENALTY SUMMARY

Section 12996.5 (b) of the Food and Agricultural Code states: "The exposure of each person to a pesticide resulting from the violation of section 12972 or 12973, or any regulation adopted pursuant to section 12976, 12981, or 14005, that causes acute illnesses or injury, shall constitute a separate violation of the statute or regulation."

The Agricultural Commissioner proposes to fine you $3,000.00 each for five (5) separate counts of the above described violation for a total of $15,000.00. The violation is considered a Class "A" violations. Class "A" violations are violations of a law or regulation that caused a health, property, or environmental hazard. Sun Pacific Farming-Maricopa caused a hazard to the health of workers, property, and the environment by not applying Vulcan® in a careful and effective manner. Sun Pacific Farming-Maricopa applied the pesticide Vulcan® in a manner which resulted in drift of the product onto Dan Andrews Farms LLC cabbage site 57C leading five field workers to seek medical attention.

The fine range for a Class "A" violation is $700.00 to $5,000.00. This fine for five (5) separate violations of 3 CCR section 6600(b) was placed at $3,000.00 of the fine range each for a total fine of $15,000.00, due to acute illness experienced by five of the fieldworkers requiring medical attention, caused by the alleged pesticide exposure. The $3,000.00 fine range is applied five times, once for each individual.

CODE SECTION VIOLATED

Title 3 California Code of Regulations Section 6600(b) states:

Each person performing pest control shall:

(b) Perform all pest control in a careful and effective manner.

VIOLATION V

On May 11, 2017, a Pest Control Headquarters and Employee Safety Inspection number 109-15-17-M007-001 was conducted on Sun Pacific Farming-Maricopa. During the inspection, the following noncompliance was found: There was no record of a medical evaluation for the use of

a respirator for three of the applicators – Manuel Rivera, Artemio Gonzales and Alfredo Garcia. Sun Pacific Farming – Maricopa violated California Code of Regulations Section 6739(d)(5)(A) by failing to ensure that medical evaluations were conducted on their employees before the employee was required to use a respirator.

PENALTY SUMMARY

The Agricultural Commissioner proposes to fine you $250.00 for the above described violation. The violation is considered a Class "B" violations. Class "B" violations are violations of a law or regulation that mitigates the risk of adverse health, property, or environmental effects.

The fine range for a Class "B" violation is $250.00 to $1,000.00. This fine for a violation of the 3 CCR Section 6739(d)(5)(A) 600(b) was placed at the bottom of the fine range due to the Respondents lack of prior history in file.

CODE SECTION VIOLATED

Title 3 California Code of Regulations - Respiratory Protection - Section 6739(d)(5)(A) states:

(d) Medical Evaluation. The employer shall ensure a medical evaluation is conducted to determine the employee's ability to use a respirator before the employee is fit tested or required to use the respirator in the workplace. The employer may discontinue an employee's medical evaluations when the employee is no longer required to use a respirator.

(5) Medical Determination.

(A) The employer shall obtain a written medical recommendation from the PLHCP regarding the employee's ability to use the respirator. The written medical recommendation shall be provided on the form in subsection (s) or provide substantially the same information as follows:

1. Any limitations on respirator use related to the medical condition of the employee, or relating to the workplace conditions in which the respirator will be used, including whether or not the employee is medically able to use the respirator;

2. The need, if any, for follow-up medical evaluations; and

3. A statement that the PLHCP has provided the employee with a copy of the PLHCP's written medical recommendation.

OTHER RELEVANT CODE SECTIONS

Food and Agricultural Code Section 12996.5 states:

(a) For the purposes of this chapter:

(1) "Office" means the Office of Environmental Health Hazard Assessment.

(2) "Department" means the Department of Pesticide Regulation.

(3) "Certified Unified Program Agency" or "CUPA" means the agency certified by the Secretary for Environmental Protection to implement the unified program specified in Chapter 6.11 (commencing with Section 25404) of Division 20 of the Health and Safety Code within a jurisdiction.

(4) "Agency" means the California Environmental Protection Agency.

(5) "Nonoccupational" means that the person exposed to the pesticide was not at the time of the exposure performing work as an employee.

(6) "Acute" means a medical condition that involves a sudden onset of symptoms due to an illness, injury, or other medical problem that requires prompt medical attention and that has a limited duration.

(7) "Uncompensated medical care" means the cost of care not covered by any other program, including, but not limited to copayments for medical insurance, Healthy Families Program, or Medi-Cal. Reimbursed medical costs shall not exceed 125 percent of the Medi-Cal reimbursement rates.

(b) The exposure of each person to a pesticide resulting from the violation of Section 12972 or 12973, or any regulation adopted pursuant to Section 12976, 12981, or 14005, that causes acute illnesses or injury, shall constitute a separate violation of the statute or regulation.

The amount of this fine was determined by applying the circumstances of the violation to the fine regulations adopted for use in these actions. These regulations are found in Title 3, California Code of Regulations (3 CCR), section 6130 which provides:

6130. Civil Penalty Actions by Commissioners

(a) When taking civil penalty action on incidents or violations related to agricultural or structural use of pesticides and all uses of fumigants pursuant to section 12999.5 of the Food and Agricultural Code, county agricultural commissioners shall use the provisions of this section to determine the violation class and the fine amount. This section may also be used to determine the violation class and fine amount for violations involving other uses of pesticides.
(b) County agricultural commissioners shall designate violations as "Class A," "Class B," or "Class C" using the following definitions:

(1) A Class A violation is one of the following:
(A) A violation that caused a health, property, or environmental hazard.
(B) A violation of a law or regulation that mitigates the risk of adverse health, property, or environmental effects, and the commissioner determines that one of the following aggravating circumstances support elevation to Class A.
1. The respondent has a history of violations;
2. The respondent failed to cooperate in the investigation of the incident or allow a lawful inspection; or,
3. The respondent demonstrated a disregard for specific hazards of the pesticide used;
(C) A violation of a lawful order of the commissioner issued pursuant to sections 11737, 11737.5, 11896, 11897, or 13102 of the Food and Agricultural Code.
(2) A Class B violation is a violation of a law or regulation that mitigates the risk of adverse health, property, or environmental effects that is not designated as Class A.
(3) A Class C violation is a violation of a law or regulation that does not mitigate the risk of an adverse health, property, or environmental effect, including, but not limited to, Title 3, California Code of Regulations, sections 6624 through 6628, and Food and Agricultural Code sections 11732, 11733, and 11761.

(c) The fine range for each class of violation is:
(1) Class A: $700 to $5,000.
(2) Class B: $250 to $1,000.
(3) Class C: $50 to $400.

(d) When determining the fine amount within the fine range, the commissioner shall use relevant facts, including severity of actual or potential effects and the respondent's compliance history, and include those relevant facts in the notice of proposed action.

(e) The commissioner shall send a copy of the notice of proposed action to the Director no later than the time the notice is provided to the respondent.

(f) If the respondent requested and appeared at the hearing offered by the commissioner, the commissioner's decision shall include information concerning the person's right to appeal the decision to the Director.

(g) The commissioner shall send a copy of the notice of final action to the Director no later than the time the notice is provided to the respondent.

PESTICIDE INCIDENT REIMBURSEMENT NOTICE – FAC SECTION 12997.5

Any person found in violation of pesticide laws and regulations that resulted in illness or injury requiring emergency medical transport or emergency medical treatment of any individual, in a non-occupational setting, from a pesticide used in the production of an agricultural commodity shall be liable to the individual harmed or to the medical provider for the immediate costs of uncompensated medical care from acute injuries and illnesses of the exposed individual.

TIMELY REIMBURSEMENT – PENALTY OFFSET AND PROOF NOTICE – FAC SECTIONS 12996.5 AND 12997.5

If you offer to reimburse, or have already reimbursed, the immediate medical costs for acute medical illnesses and injury, the Commissioner may reduce the proposed administrative civil penalty by an amount up to fifty percent. You must request a hearing and provide proof at the hearing of immediate reimbursement in order for the Commissioner to consider reducing the penalty.

YOU MAY REVIEW THE EVIDENCE AGAINST YOU
You are entitled to review the Agricultural Commissioner's evidence supporting these charges during the regular business hours at the office of the Kern County Department of Agriculture and Measurement Standards, 1001 South Mount Vernon Avenue, Bakersfield, California 93307.

YOU MAY REQUEST A HEARING AND PRESENT EVIDENCE AT THE HEARING
You may request a hearing to review the Commissioner's evidence, and to present any evidence, oral or written, on your behalf as to why the Commissioner should not take the proposed action. The attached handout, "Preparing for Your Administrative Pesticide Penalty Hearing," has more information about the hearing process. A copy of this pamphlet can also be obtained at. You are not required to be represented by legal counsel at the hearing. Your attorney may accompany you and represent you if you wish. You will be provided a written decision of the Commissioner's finding. Although not required by the authorizing statute, a recording will be made of the hearing proceedings. If you require a translator at the hearing, you must inform the Commissioner within 20 days before the scheduled hearing date.

HOW TO REQUEST A HEARING - FAILURE TO REQUEST – FAC SECTION 12999.5
A hearing in this matter will be scheduled and held at the office of the Kern County Department of Agriculture and Measurement Standards, located at the above noted address, if you request a hearing in writing within 20 days after receipt of this Notice of Proposed Action.

FAILURE TO TIMELY REQUEST A HEARING IS A WAIVER OF THE RIGHT TO A HEARING. THE COMMISSIONER MAY TAKE THE ACTION PROPOSED IN THIS NOTICE WITHOUT A HEARING. FURTHERMORE, FAILURE TO REQUEST A

HEARING OR ATTEND THE HEARING AT THE SCHEDULED TIME AND DATE IS A WAIVER OF YOUR RIGHT TO APPEAL THE COMMISSIONER'S DECISION AND ORDER.

STIPULATION AND WAIVER TO ORDER – FAC SECTION 12999.5

If you do not wish to request a hearing to contest the charges and proposed action, you may stipulate (agree) to the enclosed Order by dating, signing, and returning the enclosed Stipulation and Waiver to Order within 20 days of receipt of this notice.

APPEAL RIGHTS AFTER HEARING – FAC SECTION 12999.5

Should you disagree with the Commissioner's decision, you may request an appeal to the Director of DPR within 30 days of receiving the Commissioner's decision and order. However, you waive these appeal rights if you do not request and attend the hearing at the scheduled time and date, or if you fail to request an appeal within the 30-day time frame.

The request for appeal must be mailed to the Director of the Department of Pesticide Regulation, 1001 I Street, P.O. Box 4015, Sacramento, California 95812-4015.

The request for appeal:

1. Must be signed by you or your authorized agent; and
2. Must state the grounds for the appeal; and
3. Must include a copy of the Commissioner's Decision and Order; and
4. Must be filed or mailed to the Commissioner at the same time you mail it to the Director.

Failure to follow any of the above requirements may affect your right to appeal.

If the Director grants an appeal, you will receive the Director's written decision approximately 45 days after receipt of your appeal, or as soon thereafter as practical.

If you have any questions regarding this matter, please feel free to contact Deputy Director, Lanette Bankston at (661)868-6300.

Dated: 7/31/17

Glenn Fankhauser
Kern County Agricultural Commissioner/Sealer

STATE OF CALIFORNIA
DEPARTMENT OF PESTICIDE REGULATION

PESTICIDE EPISODE CLOSING REPORT

DPR-ENF-055 (REV. 03/14)
PAGE 1 OF 2

AMENDED? ☐ YES ☒ NO

PAGE 1 OF 2

DPR ENFORCEMENT BRANCH
1001 I STREET, P.O. BOX 4015
SACRAMENTO, CALIFORNIA 95812-4015
www.cdpr.ca.gov

PRIORITY EPISODE NUMBER	NOTIFICATION DATE	DATE OF OCCURRENCE
34-KER-17	05/05/2017	05/05/2017

BRAND NAME OF PESTICIDE/ACTIVE INGREDIENT	REGISTRATION NUMBER FROM LABEL	RESTRICTED USE?
Vulcan / chlorpyrifos	66222-233-AA	☒ YES ☐ NO ☐ UNKNOWN
Cosavet DF / Sulfur	70905-1-AA	☐ YES ☒ NO ☐ UNKNOWN
Toledo 45WP Agricultural Fungicide / tebuconazole	83100-13-AA-83979	☐ YES ☒ NO ☐ UNKNOWN
Sevin Brand XLR Plus Carbaryl Insecticide / carbaryl	61842-37-AA	☒ YES ☐ NO ☐ UNKNOWN
Reaper Clearform / abamectin	34704-1078-ZA	☐ YES ☒ NO ☐ UNKNOWN

SUMMARY OF FINDINGS *(Continue on page 2, if necessary)*:

Additional Pesticides:

Sniper / Bifenthrin	34704-1078-AA	Not Restricted Use
Activator 90 / None	34704-50034	Not Restricted Use
Amid-Thin W / 1-naphthaleneacetamide	5481-426-AA	Not Restricted Use

On May 5, 2017, three crews of workers, totaling 48 individuals, were harvesting cabbage in a field operated by Dan Andrews Farms LLC when some fieldworkers reported experiencing symptoms. Some fieldworkers smelled an odor, described as tar or gasoline like, while traveling near or upon arrival to the cabbage field to begin their workday harvesting cabbage. At around 6:30 to 7:30 a.m., the odor progressively worsened and 37 of the workers experienced symptoms that were believed to be caused by the odor. The symptoms reported included nausea, headache, numbness of lips and tongue, sweating, chills, and shakiness. One fieldworker became dizzy, nauseous, vomited, and fainted by the field. The fieldworker that fainted was transported by ambulance to Mercy Hospital Southwest after the Kern County Fire Department responded to the site to provide medical assessment and decontamination if warranted.

During the investigation, Kern CAC staff found that beginning at 6:00 p.m. on May 4, 2017, through the morning of May 5, 2017, four property operators performed pesticide applications to fields located between 1/2 mile to 1 1/2 mile from the cabbage field being harvested. Sun Pacific Farming - Maricopa made applications of Vulcan to seven seedless tangerine sites located between 1/2 mile to 1 1/2 mile west and northwest of the cabbage field. Langer Farms, LLC made an application of Sevin XLR Plus, Amid-Thin W, and Activator 90 to an apple site located 1/2 mile north of the cabbage site. Grape Man Farms, LP made an application of Toledo 45 WP and Cosavet DF to two grape sites located 1/2 mile northwest of the cabbage site. Dan Andrews Farms LLC made an application of Reaper Clearform and Sniper to a watermelon site located 1/2 mile southwest of the cabbage field.

Kern CAC staff collected foliage samples in order to establish a possible drift from the applications that had occured the evening prior and the morning of the incident. Analysis performed by the CDFA Center for Analytical Chemistry reported the presence of chlorpyrifos (A.I. of Vulcan) in a gradient pattern from a Sun Pacific Farming - Maricopa seedless tangerine site to the cabbage field the workers were harvesting. Analysis of another set of foliage samples reported the presence of sulfur (A.I. of Cosavet D.F.) in a gradient pattern from Grape Man Farms, LP grape site to the cabbage site the workers were harvesting.

(Over)

STATE OF CALIFORNIA
DEPARTMENT OF PESTICIDE REGULATION

PESTICIDE EPISODE CLOSING REPORT

DPR-ENF-055 (REV. 03/14) (REVERSE)
PAGE 2 OF 2

DPR ENFORCEMENT BRANCH
1001 I STREET, P.O. BOX 4015
SACRAMENTO, CALIFORNIA 95812-4015
www.cdpr.ca.gov

PRIORITY EPISODE NUMBER	NOTIFICATION DATE	DATE OF OCCURRENCE
34-KER-17	05/05/2017	05/05/2017

SUMMARY OF FINDINGS, CONTINUED *(Continue on supplemental form DPR-ENF-116, if necessary)*:

Administrative Civil Penalty Details:
Grape Man Farms, LP:
• 12973 FAC: Failure to follow label directions to not apply when weather conditions favored drift from the treatment area.
• 6600(b): Failure to perform pest control in a careful and effective manner.
• 6614(b)(2): Making an application when there was a reasonable possibility of damage to nontarget crops, animals, or other public or private property.
• 009-ACP-KER-17/18 Proposed Action $20,000

ADMINISTRATIVE CIVIL PENALTY DETAILS (*See CA Pesticide Priority Episode Handling Manual*):
Sun Pacific Farming – Maricopa:
• 12973 FAC: Failure to follow the Vulcan label directions pertaining to nozzle size, drift prevention requirements, and to not allow contact with people and nontarget crops.
• 6600(b) CCR: Failure to perform pest control in a careful and effective manner.
• 6739(d)(5)(A) CCR: Failure to obtain a medical recommendation from a PLHCP for three employees regarding the employee's ability to use a respirator prior to handling a product requiring the use of a respirator.
• 6614(b)(3) CCR: Making an application when there was a reasonable possibility of contamination of nontarget public or private property, including the creation of a health hazard.
• 010-ACP-KER-17/18 Proposed Action $30,250

OTHER ENFORCEMENT ACTION:

☐ COMPLIANCE ACTION: _____

☐ REFERRAL: _____

☒ PENDING: ACP 07/31/2017

INVESTIGATION CONSIDERATIONS / IMPACTS / EFFECTS:			
PUBLIC HEALTH	☒ YES	☐ NO	☐ N/A
GROUND WATER	☐ YES	☒ NO	☐ N/A
WORKER HEALTH AND SAFETY	☒ YES	☐ NO	☐ N/A
ENDANGERED SPECIES	☐ YES	☒ NO	☐ N/A
PRODUCT REGISTRATION	☒ YES	☐ NO	☐ N/A
CANCELLED / SUSPENDED PESTICIDE	☐ YES	☒ NO	☐ N/A

AGENCY NOTIFICATION

U.S. EPA: Ms. Fabiola Estrada
CAC: Mr. Glenn Fankhauser
DIR: Ms. Amalia Neidhardt
CDPH: Dr. Justine Weinberg
OEHHA: Dr. William Ngai, Dr. James Nakashima
CalEPA:
OTHER:
OTHER:
DATE SENT: 12/18/2017

DPR ROUTING:
Benson, Byerly, Cuevas, Everett, Fadipe, Ford, Frenkel, Guerra, Hughes, James, Lopez, Marade, Marciano, McCarthy, Motakef, Naef, Ogawa, Oriel, Perez, Richmond, Ross, Sarracino, Solari, Thalken, Verder-Carlos

112017

REPORT PREPARED BY	TELEPHONE NUMBER *(Include Area Code)*	DATE
Jose Bueno	559-297-5423	12/15/2017
DPR R.O. MANAGER'S SIGNATURE	**TELEPHONE NUMBER *(Include Area Code)***	**DATE**
Louie Flores	559-297-3511	12/18/2017

FOR PUBLICATION

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

IN RE PESTICIDE ACTION NETWORK NORTH AMERICA; NATURAL RESOURCES DEFENSE COUNCIL, INC.,	No. 14-72794
PESTICIDE ACTION NETWORK NORTH AMERICA; NATURAL RESOURCES DEFENSE COUNCIL, INC., *Petitioners*, v. U.S. ENVIRONMENTAL PROTECTION AGENCY, *Respondent*.	ORDER

Filed July 18, 2017

Before: Diarmuid F. O'Scannlain, A. Wallace Tashima, and M. Margaret McKeown, Circuit Judges.

SUMMARY*

Mandamus

The panel denied the motion for further mandamus relief filed by Pesticide Action Network North America and Natural Resources Defense Council, which alleged that the United States Environmental Protection Agency ("EPA")'s denial of the Council's administrative petition, seeking to revoke all food tolerances and cancel all registration of a pesticide called chlorpyifos, was inadequate.

In a published order on August 10, 2015, the panel ordered EPA to respond to the Council's administrative petition. In a subsequent published order, the panel directed EPA to take "final action" by March 31, 2017. The EPA denied the Council's petition on March 29, 2017.

The Council filed the present mandamus motion asserting that EPA's denial was inadequate because it contained no new safety findings, and made no final determination as to whether chlorpyifos food tolerances must be revoked.

The panel held that EPA had complied with the panel's previous orders by issuing a "final response to the petition." The panel further held that the Council's mandamus motion was premature, and its substantive objections to the EPA's denial must first be made through the administrative process mandated by statute.

* This summary constitutes no part of the opinion of the court. It has been prepared by court staff for the convenience of the reader.

COUNSEL

Patti A. Goldman and Kristen Boyles, Earthjustice, Seattle, Washington, for Petitioners.

Erica M. Zilioli, Environmental Defense Section; Jeffrey H. Wood, Acting Assistant Attorney General, Environment & Natural Resources Division; United States Department of Justice, Washington, D.C.; Mark Dyner, Office of General Counsel; United States Environmental Protection Agency, Washington, D.C.; for Respondents.

Stanley H. Abramson, Donald C. McLean, Kathleen R. Heilman, and Sylvia G. Costelloe, Arent Fox LLP, Washington, D.C., for Amici Curiae Dow Agrosciences LLC.

ORDER

In 2007, Pesticide Action Network North America and Natural Resources Defense Council (collectively, "PANNA") filed an administrative petition with the United States Environmental Protection Agency ("EPA"). The petition sought to revoke all food tolerances and cancel all registration of a pesticide called chlorpyifos. In 2014, having grown frustrated with EPA's inertia, PANNA petitioned this court for a writ of mandamus to force the agency to issue a response, which PANNA acknowledged could include "a final denial order . . . if that is how EPA decides to resolve [it]."

On August 10, 2015, we ordered EPA to "issue *either* a proposed or final revocation rule *or* a full and final response" to PANNA's administrative petition. *In re Pesticide Action*

Network N. Am., 798 F.3d 809, 814 (9th Cir. 2015) (emphasis added). We later directed EPA to "take final action" on the petition by March 31, 2017. *In re Pesticide Action Network N. Am.*, 840 F.3d 1014, 1015 (9th Cir. 2016).

EPA denied the petition on March 29, 2017. *See* 82 Fed. Reg. 16,581 (Apr. 5, 2017). PANNA promptly filed a motion for "further mandamus relief," asserting that EPA's denial was inadequate because it contained "no new safety findings" and no "final determination as to whether chlorpyifos food tolerances must be revoked." In short—and in its own words—PANNA's motion faulted EPA for "fail[ing] to act *on the substance* of the petition."

PANNA's complaints arrive at our doorstep too soon. Although we previously condemned EPA's "egregious" delay in responding to PANNA's petition, the agency has now complied with our orders by issuing a "final response to the petition." *See In re Pesticide Action Network N. Am.*, 798 F.3d at 811; *see also* 21 U.S.C. § 346a(d)(4)(A)(iii) (providing that one valid agency response to a petition challenging a pesticide's tolerances is to "issue an order denying the petition").

These mandamus proceedings have addressed the *timing*, not the *substance*, of EPA's response. *See In re Pesticide Action Network N. Am.*, 798 F.3d at 813 ("The only question before us is whether EPA's delay in responding to the administrative petition warrants the extraordinary remedy of mandamus."). Now that EPA has issued its denial, substantive objections must first be made through the administrative process mandated by statute. *See* 21 U.S.C. §§ 346a(g)(2), (h)(1); 40 C.F.R. §§ 178.65, 180.30(b). PANNA implicitly recognizes as much by acknowledging

that "[f]iling objections and awaiting their resolution by the EPA Administrator is a prerequisite to obtaining judicial review" of EPA's final response to the petition. Only at that point may we consider the merits of EPA's "final agency action." *See* 5 U.S.C. § 704. Although EPA dragged its heels for nearly a decade, it has now done what we ordered it to do.

PANNA's motion for further mandamus relief is **DENIED**.

STATE OF CALIFORNIA
DEPARTMENT OF PESTICIDE REGULATION

PESTICIDE EPISODE 15-DAY REPORT

DPR-ENF-115 (REV. 03/14)
PAGE 1 OF 1

AMENDED? ☐ YES ☒ NO

PAGE 1 OF 1

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PRIORITY EPISODE NUMBER	DATE OF OCCURRENCE	NOTIFICATION DATE	PRIORITY EPISODE 15-DAY REPORT DUE DATE
52-SOL-18	7/26/2018	7/27/2018	8/16/2018

BRAND NAME OF PESTICIDE/ACTIVE INGREDIENT	REGISTRATION NUMBER FROM LABEL	RESTRICTED USE?		
Besiege Insecticide/Lambda-cyhalothrin	100-1402	☒ YES	☐ NO	☐ UNKNOWN
Onager Optek/Hexythiazox	10163-337	☐ YES	☒ NO	☐ UNKNOWN
Warhawk/chlorpyrifos	34704-857	☒ YES	☐ NO	☐ UNKNOWN
Freeway/Oxyethlene	34704-50031	☐ YES	☒ NO	☐ UNKNOWN
		☐ YES	☐ NO	☐ UNKNOWN

SUMMARY OF THE CURRENT STATUS OF THE EPISODE *(County Agricultural Commissioner's initial findings)*:

On July 26, 2018, Solano County Agricultural Commissioner's (CAC) Office received a call from [redacted], stating that 10 fieldworkers from Four Leaf Farm Labor Contractor (FLC) displayed symptoms such as vomiting, numbness, and itchy throats while weeding in the northeast corner of his sunflower field. At the same time, Premier Ag Services Pest Control Business was applying by airblast sprayer to an almond orchard in the field adjacent to the fieldworkers. Solano CAC is investigating.

CAC staff have conducted interviews with employees of 4Leaf FLC that experienced symptoms. The CAC staff have also conducted interviews of employees of Premier Ag Services Pest Control Business who were involved in an application suspected to have resulted in the symptoms experienced by the 4Leaf employees.
A number of sample have been collected, consisting of swab samples and a gradient of foliar and vegetation samples. These samples have been submitted for laboratory analysis and the CAC is currently awaiting the results.
The CAC will continue to investigate.

SUSPECTED VIOLATIONS *(Include brief description)*:

Undetermined at this time.

PRIORITY EPISODE INVESTIGATION REPORT PROJECTED COMPLETION DATE: Unknown at this time

DPR ROUTING:

Benson, Byerly, Coleman, Everett, Fadipe, Farnsworth, Francone, Frenkel, Guerra, Hughes, Jetter, Lee, Lopez, Marade, Marciano, Motakef, Ogawa, Oriel, Papathakis, Richmond, Ross, Sarracino, Shattuck, Solari, Tehrani, Verder-Carlos, Yanga

080315

AGENCY NOTIFICATION

U.S.EPA: Ms. Fabiola Estrada

OTHER: CAC Simone Hardy

REPORT PREPARED BY *(Please print)*:	TELEPHONE NUMBER *(Incl. Area Code)*	DATE SENT:
Dennis Whitley	(916) 376-8963	8/17/2018

SIMONE HARDY
Agricultural Commissioner /
Sealer of Weights and Measures

JOSE ARRIAGA
Assistant Agricultural Commissioner /
Sealer of Weights and Measures

www.solanocounty.com

COUNTY AGRICULTURAL COMMISSIONER /
SEALER OF WEIGHTS AND MEASURES

SOLANO COUNTY

OFFICE LOCATION:
2543 Cordelia Road
Fairfield, CA 94534

MAILING ADDRESS:
675 Texas Street
Fairfield, CA 94533

Phone (707) 784-1310
Fax (707) 784-1330

November 5, 2018

Lipton, Eric [redacted]

RE: Public Records Act Request, Pesticide Episode 15-Day Report 52-SOL-18

Redacted are identities (complainant and alleged violator) under Gov. Code section 6254, subdivision (k), which exempts "[r]ecords, the disclosure of which is exempted or prohibited pursuant to federal or state law, including, but not limited to, provisions of the Evidence Code relating to privilege."

Simone Hardy

Agricultural Commissioner/Sealer of Weights and Measures

FOR PUBLICATION

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

LEAGUE OF UNITED LATIN AMERICAN CITIZENS; PESTICIDE ACTION NETWORK NORTH AMERICA; NATURAL RESOURCES DEFENSE COUNCIL; CALIFORNIA RURAL LEGAL ASSISTANCE FOUNDATION; FARMWORKERS ASSOCIATION OF FLORIDA; FARMWORKER JUSTICE GREENLATINOS; LABOR COUNCIL FOR LATIN AMERICAN ADVANCEMENT; LEARNING DISABILITIES ASSOCIATION OF AMERICA; NATIONAL HISPANIC MEDICAL ASSOCIATION; PINEROS Y CAMPESINOS UNIDOS DEL NOROESTE; UNITED FARM WORKERS, *Petitioners*, STATE OF NEW YORK; STATE OF MARYLAND; STATE OF VERMONT; STATE OF WASHINGTON; COMMONWEALTH OF MASSACHUSETTS; DISTRICT OF COLUMBIA; STATE OF CALIFORNIA; STATE OF HAWAII, *Intervenors*, v.	No. 17-71636 OPINION

ANDREW WHEELER, Acting Administrator of the U.S. Environmental Protection Agency; and U.S. ENVIRONMENTAL PROTECTION AGENCY,

Respondents.

On Petition for Review of an Order of the Environmental Protection Agency

Argued and Submitted July 9, 2018
Seattle, Washington

Filed August 9, 2018

Before: Ferdinand F. Fernandez and Jacqueline H. Nguyen, Circuit Judges, and Jed S. Rakoff,* District Judge.

Opinion by Judge Rakoff;
Dissent by Judge Fernandez

* The Honorable Jed S. Rakoff, United States District Judge for the Southern District of New York, sitting by designation.

SUMMARY[**]

Pesticides

The panel granted a petition for review, and vacated the Environmental Protection Agency's ("EPA") 2017 order maintaining a tolerance for the pesticide chlorpyrifos, and remanded to the EPA with directions to revoke all tolerances and cancel all registrations for chlorpyrifos within 60 days.

The Federal Food, Drug, and Cosmetic Act ("FFDCA") authorizes the EPA to regulate the use of pesticides on foods according to specific statutory standards, and grants the EPA a limited authority to establish tolerances for pesticides meeting statutory qualifications. The EPA is subject to safety standards in exercising its authority to register pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA").

The EPA argued that FFDCA's section 346a(g)(2)'s administrative process deprived this Court of jurisdiction until the EPA issues a response to petitioner's administrative objections under section 346a(g)(2)(C), which it has not done to date.

The panel held that section 346a(h)(1) of the FFDCA does not "clearly state" that obtaining a section (g)(2)(C) order in response to administrative objections is a jurisdictional requirement. The panel held that section 346a(h)(1) contains no jurisdictional label, is structured as a

[**] This summary constitutes no part of the opinion of the court. It has been prepared by court staff for the convenience of the reader.

limitation on the parties rather than the court, and only references an exhaustion process that is outlined in a separate section of the statute.

The panel held that in light of the strong individual interests against requiring exhaustion and weak institutional interests in favor of it, petitioners need not exhaust their administrative objections and were not precluded from raising issues on the merits.

Turning to the merits, the panel held that there was no justification for the EPA's decision in its 2017 order to maintain a tolerance for chlorpyrifos in the face of scientific evidence that its residue on food causes neurodevelopmental damage to children. The panel further held that the EPA cannot refuse to act because of possible contradiction in the future by evidence. The panel held that the EPA was in direct contravention of the FFDCA and FIFRA.

Judge Fernandez dissented. Judge Fernandez would hold that there is no jurisdiction over the petition for review under FFDCA and FIFRA, and dismiss the petition.

COUNSEL

Patti A. Goldman (argued), Marisa C. Ordonia, and Kristen L. Boyles, Earthjustice, Seattle, Washington, for Petitioners.

Frederick A. Brodie (argued), Assistant Solicitor General; Andrea Oser, Deputy Solicitor General; Barbara D. Underwood, Attorney General; Office of the Attorney General, Albany, New York; Brian E. Frosh, Attorney General; Steven M. Sullivan, Solicitor General; Office of the Attorney General, Baltimore, Maryland; Thomas J. Donovan Jr., Attorney General; Nicholas F. Persampieri, Assistant Attorney General; Office of the Attorney General, Montpelier, Vermont; Robert W. Ferguson, Attorney General; William R. Sherman, Counsel for Environmental Protection; Attorney General's Office, Seattle, Washington; Maura Healey, Attorney General; I. Andrew Goldberg, Assistant Attorney General; Environmental Protection Division, Office of the Attorney General, Boston, Massachusetts; Karl A. Racine, Attorney General; Brian R. Caldwell, Assistant Attorney General; Office of the Attorney General, Washington, D.C.; Xavier Becerra, Attorney General; Susan S. Fiering, Supervising Deputy Attorney General; Reed Sato, Deputy Attorney General; Office of the Attorney General, Sacramento, California; Russell A. Suzuki, Acting Attorney General; Wade H. Hargrove III, Deputy Attorney General; Health and Human Services Division, Department of the Attorney General, Honolulu, Hawaii; for Intervenors.

Phillip R. Dupré (argued) and Erica M. Zilioli, Attorneys, Environmental Defense Section; Jeffrey H. Wood, Acting Assistant Attorney General; Environment and Natural Resources Division, United States Department of Justice, Washington, D.C.; Mark Dyner, Office of the General

Counsel, United States Environmental Protection Agency, Washington, D.C.; for Respondents.

Donald C. McLean, Stanley H. Abramson, Kathleen R. Heilman, and Sylvia G. Costelloe, Arent Fox LLP, Washington, D.C., for Amicus Curiae Dow Agrosciences LLC.

Susan J. Kraham and Edward Lloyd, Columbia Environmental Clinic, Morningside Heights Legal Services, New York, New York, for Amicus Curiae Congressman Henry Waxman.

Shaun A. Goho, Emmett Environmental Law & Policy Clinic, Harvard Law School, Cambridge, Massachusetts, for Amici Curiae Health Professional Organizations.

OPINION

RAKOFF, District Judge:

Over nearly two decades, the U.S. Environmental Protection Agency ("EPA") has documented the likely adverse effects of foods containing the residue of the pesticide chlorpyrifos on the physical and mental development of American infants and children, often lasting into adulthood. In such circumstances, federal law commands that the EPA ban such a pesticide from use on food products unless "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide." 21 U.S.C. § 346a(b)(2)(A)(ii). Yet, over the past decade and more, the EPA has stalled on banning chlorpyrifos, first by largely ignoring a petition properly filed pursuant to law seeking such a ban, then by temporizing in response to repeated orders by this Court to respond to the petition, and, finally, in its latest tactic, by denying outright our jurisdiction to review the ultimate denial of the petition, even while offering no defense on the merits. If Congress's statutory mandates are to mean anything, the time has come to put a stop to this patent evasion.

Petitioners seek review of an EPA order issued March 29, 2017 (the "2017 Order" or "Order") that denied a 2007 petition to revoke "tolerances," i.e. limited allowances, for the use of chlorpyrifos on food products. Petitioners argue that the EPA does not have the authority to maintain the tolerances for chlorpyrifos under the Federal Food, Drug, and Cosmetic Act ("FFDCA"), which authorizes the EPA to "leave in effect a tolerance for a pesticide chemical residue in or on a food only if the Administrator determines that the tolerance is safe"—with "safe," in turn, defined to mean that the EPA "has determined that there is a reasonable certainty that no harm will result from aggregate exposure to the

pesticide chemical residue." 21 U.S.C. § 346a(b)(2)(A)(i)–(ii). Respondent, the EPA, has never made any such determination and, indeed, has itself long questioned the safety of permitting chlorpyrifos to be used within the allowed tolerances. The EPA, therefore, does not defend the 2017 Order on the merits. Instead, the EPA argues that, despite petitioners having properly-filed administrative objections to the 2017 Order more than a year ago, and despite the statutory requirement that the EPA respond to such objections "as soon as practicable," the EPA's utter failure to respond to the objections deprives us of jurisdiction to adjudicate whether the EPA exceeded its statutory authority in refusing to ban use of chlorpyrifos on food products.

We hold that obtaining a response to objections before seeking review by this Court is a claim-processing rule that does not restrict federal jurisdiction, and that can, and here should, be excused. There being no other reason not to do so, we grant the petition on the merits.

BACKGROUND

A. *The Statutory Framework*

The FFDCA authorizes the EPA to regulate the use of pesticides on foods according to specific statutory criteria. 21 U.S.C. §§ 301–399i. The FFDCA prescribes that food with "any pesticide chemical residue . . . shall be deemed unsafe" and barred from movement in interstate commerce. *Id.* § 346a(a)(1). However, it grants the EPA a limited authority to establish tolerances for pesticides meeting statutory qualifications, enabling foods bearing residues of those pesticides within these tolerances to move in interstate commerce. *See id.* § 346a(a), (a)(4), (b)(1).

The EPA's ability to establish tolerances depends on a safety finding. "The Administrator may establish or leave in effect a tolerance . . . only if the Administrator determines that the tolerance is safe." *Id.* § 346a(b)(2)(A)(i). A tolerance qualifies as safe if "the Administrator has determined that there is a *reasonable certainty* that *no* harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." *Id.* § 346a(b)(2)(A)(ii) (emphasis added). To make such a determination, the EPA must perform a safety analysis to "ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure" and "publish a specific determination regarding the safety of the pesticide chemical residue for infants and children. *Id.* § 346(b)(2)(C)(ii)(I)–(II). Furthermore, even after establishing a tolerance, the EPA bears continuous responsibility to ensure that the tolerance continues to satisfy the FFDCA's safety standard; the FFDCA provides that the Administrator may "leave in effect a tolerance . . . only if the Administrator determines that the tolerance is safe" and "shall modify or revoke a tolerance if the Administrator determines it is not safe." *Id.* § 346a(b)(2)(A)(i).

The EPA is subject to these same safety standards in exercising its authority to register pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA"). *See* 7 U.S.C. § 136a(a). The EPA Administrator must register a pesticide—which is a requirement for pesticides to be distributed or sold—when, among other qualifications, the pesticide does not have "unreasonable adverse effects on the environment." *Id.* § 136a(c)(5) (D). FIFRA incorporates the FFDCA's safety standard into the definition of "unreasonable adverse effects" to include "a human dietary risk from residues that result from a use of a

pesticide in or on any food inconsistent with the standard under [the FFDCA]." *Id.* § 136(bb). FIFRA requires the EPA to reevaluate pesticides periodically after approval. *Id.*

While the EPA can act on its own initiative to establish, modify or revoke a tolerance under the FFDCA, 21 U.S.C. § 346a(e)(1), "[a]ny person may file . . . a petition proposing the issuance of [such] a regulation." *Id.* § 346a(d)(1). After "due consideration," the EPA Administrator must issue either a proposed or final regulation or an order denying the petition. *Id.* § 346a(d)(4)(A). After this response, "any person may file objections thereto with the Administrator." *Id.* § 346a(g)(2)(A). The FFDCA directs that the Administrator "shall issue an order [known as a "g(2)(C) order"] stating the action taken upon each . . . objection" "[a]s soon as practicable." *Id.* § 346a(g)(2)(C). "[A]ny person who will be adversely affected" by that order or the underlying regulation "may obtain judicial review by filing in the United States Court of Appeals" a petition for review. *Id.* § 346a(h)(1).

B. *The History of this Litigation*

This case arises from a 2007 petition filed under 21 U.S.C. § 346a(d) proposing that the EPA revoke tolerances for the pesticide chlorpyrifos (the "2007 Petition" or the "Petition"). Chlorpyrifos, an organophosphate pesticide initially developed as a nerve gas during World War II, was approved in 1965 in the United States as a pesticide for agricultural, residential, and commercial purposes. Chlorpyrifos kills insects by suppressing acetelycholinestrerase, an enzyme that acts as a neurotransmitter in various organisms, including humans. The EPA has set chlorpyrifos residue tolerances for 80 food crops, including fruits, nuts, and vegetables. *See* 40 C.F.R. § 180.342. The 2007 Petition, filed by the Pesticide Action

Network North America ("PANNA") and the Natural Resources Defense Council ("NRDC"), presented scientific studies showing that children and infants who had been exposed prenatally to low doses of chlorpyrifos suffer harms such as reduced IQ, attention deficit disorders, and delayed motor development, that last into adulthood.

Prior to the Petition's filing, the EPA already had concerns about chlorpyrifos. After reviewing the registration for chlorpyrifos in 1998 under the amended FFDCA's heightened safety standards that required considering cumulative exposure and the specific risks to children, the EPA cancelled all residential uses. Although the EPA continued to allow the use of chlorpyrifos as a pesticide on food crops, *see* 40 C.F.R. § 180.342, it required that "risk mitigation measures" be implemented while a full reassessment of chlorpyrifos was undertaken, as continued usage of chlorpyrifos without additional precautions "would present risks inconsistent with FIFRA." EPA 738-R-01-007 "Interim Reregistration Eligibility Decision for Chlorpyrifos" (Feb. 2002)). This "interim reregistration" also announced future plans to reduce or revoke entirely chlorpyrifos tolerance levels for certain crops, citing "acute dietary risks" for "infants, all children, and nursing females." *Id*.

Despite these earlier expressions of concern, the EPA failed to take any decisive action in response to the 2007 Petition, notwithstanding that the EPA's own internal studies continued to document serious safety risks associated with chlorpyrifos use, particularly for children. A 2008 EPA Science Issue Paper, reviewing existing scientific studies, "preliminarily concluded that chlorpyrifos likely played a role" in low birth rate and delays in infant mental development observed in human cohort studies. A Science

Advisory Panel convened in 2008 concurred that chlorpyrifos exposures "can lead to neurochemical and behavioral alterations [in the young] that persist into adulthood." A Science Advisory Panel convened in 2011 found "persuasive" evidence "that there are enduring effects on the Central Nervous System . . . from chlorpyrifos exposure at or above 1.0 mg/kg," and that chlorpyrifos exposure is associated with adverse neurodevelopmental effects in children, including abnormal reflexes, pervasive development disorder, and attention and behavior problems.

Yet, even after all of these EPA studies, by 2012 the EPA still had not responded to the 2007 Petition. PANNA and NRDC thereupon petitioned this Court for a writ of mandamus to force the EPA to take action. We initially dismissed the mandamus petition, without prejudice to its renewal, based on the EPA's representation that it had a "concrete timeline for final agency action" to be taken on the 2007 Petition by February 2014. *In re PANNA*, 532 F. App'x 649, 651 (9th Cir. 2013). When the EPA failed to respond to the 2007 Petition by September 2014, PANNA and NRDC again petitioned for mandamus, which we granted, ordering the EPA to issue a final response on the 2007 Petition by October 2015. *In re PANNA*, 798 F.3d 809, 815 (9th Cir. 2015).[1] We found the EPA's delay in responding to the 2007 Petition "egregious," especially "[i]n view of [the] EPA's own assessment of the dangers to human health posed by this pesticide," noting that the EPA had recently "reported that chlorpyrifos poses such a significant threat to water supplies that a nationwide ban on the pesticide may be justified." *Id.* at 811, 814.

[1] Unless otherwise indicated, case quotations omit all internal quotation marks, alterations, footnotes, and citations.

Notwithstanding the deadline set by this Court, the EPA did not initially respond to the 2007 Petition until November 2015, when it issued a proposed rule revoking all tolerances for chlorpyrifos. Chlorpyrifos; Tolerance Revocations, 80 Fed. Reg. 69,080 (Nov. 6, 2015); *see* 21 U.S.C. § 346a(d)(4)(A)(ii). Describing the various scientific studies' "consistency of finding neurodevelopmental effects" as "striking," *id.* at 69,090, the EPA stated that it was "unable to conclude that the risk from aggregate exposure from the use of chlorpyrifos meets the safety standard of [21 U.S.C. § 346a(b)(2)(A)(i)]" *id.* at 69,080.

Yet the EPA still equivocated and delayed. Accordingly, in December 2015, we ordered the EPA "to take final action by December 30, 2016 on its proposed revocation rule." *In re PANNA*, 808 F.3d 402, 402 (9th Cir. 2015). In June 2016, the EPA requested a six-month extension to continue scientific analysis, a request we characterized as "another variation on a theme of partial reports, missed deadlines, and vague promises of future action that has been repeated for the past nine years." *In re PANNA*, 840 F.3d 1014, 1015 (9th Cir. 2016). We found that a six-month delay was "not justified" in light of the previous time extensions and the EPA's "continued failure to respond to the pressing health concerns presented by chlorpyrifos," but granted a three-month extension to March 2017. *Id.*

In the meantime, the EPA issued a 2016 Risk Assessment concluding that estimated dietary exposure to chlorpyrifos at existing tolerances exceeded what was acceptable for all population groups analyzed, with the highest risks for young children. The Risk Assessment found that scientific literature "as a whole provides evidence of long-lasting neurodevelopmental disorders" linked to chlorpyrifos exposure, with any remaining scientific

uncertainties insufficient to "undermine or reduce the confidence in the findings of the epidemiology studies." The EPA concluded that its analysis of chlorpyrifos "continues to indicate that the risk from the potential aggregate exposure does not meet the FFDCA safety standard" and that "expected residues of chlorpyrifos on most individual food crops exceed the 'reasonable certainty of no harm' safety standard." Chlorpyrifos; Tolerance Revocations; Notice of Data Availability and Request for Comment, 81 Fed. Reg. 81,049, 81,050 (Nov. 17, 2016).

Then, in the Order at issue in this case, the EPA reversed its position and denied the 2007 Petition on the merits, leaving chlorpyrifos tolerances in effect. Chlorpyrifos; Order Denying PANNA and NRDC's Petition To Revoke Tolerances, 82 Fed. Reg. 16,581 (Apr. 5, 2017). The Order did not refute the agency's previous scientific findings on chlorpyrifos or its conclusion that chlorpyrifos violated the FFDCA safety standard. Instead, the EPA stated that it would not revoke tolerances as "the science addressing neurodevelopmental effects remains unresolved." *Id.* at 16,583. The EPA stated that it would not complete "any associated tolerance revocation of chlorpyrifos without first attempting to come to a clearer scientific resolution," *id.*, and claimed to have "discretion to determine the schedule" for reviewing the existing chlorpyrifos tolerances as long as it completed the chlorpyrifos registration review by FIFRA's deadline of October 1, 2022, *id.* at 16,590.

PANNA and NRDC moved for further mandamus relief in this Court, arguing that the 2017 Order failed to respond adequately to the 2007 Petition. We denied their motion as premature because the EPA had "done what we ordered it to do," i.e. responded to the 2007 Petition, since the 2017 Order formally denied it. *In re PANNA*, 863 F.3d 1131, 1132 (9th

Cir. 2017). Petitioners then petitioned this Court for review of the 2017 Order. Petitioners concurrently filed objections in the EPA's administrative review process. Thereafter, we permitted several states that had also filed objections to the Order to intervene in this matter.

The EPA does not defend this suit on the merits, but argues that § 346a(g)(2)'s administrative process deprives this Court of jurisdiction until the EPA issues a response to petitioners' administrative objections, *see* § 346a(g)(2)(C), which it has not done to date.

DISCUSSION

A. *Jurisdiction*

The term "jurisdiction" refers specifically to "a court's adjudicatory authority." *Reed Elsevier, Inc. v. Muchnick*, 559 U.S. 154, 160 (2010). Therefore, "a rule should not be referred to as jurisdictional unless it governs a court's adjudicatory capacity, that is, its subject-matter or personal jurisdiction." *Henderson ex rel. Henderson v. Shinseki*, 562 U.S. 428, 435 (2011). In other words, "jurisdictional statutes speak to the power of the court rather than to the rights or obligations of the parties." *Landgraf v. USI Film Prods.*, 511 U.S. 244, 274 (1994).

The Supreme Court has emphasized the necessity of observing "the important distinctions between jurisdictional prescriptions and claim-processing rules." *Reed Elsevier*, 559 U.S. at 161. Claim-processing rules "seek to promote the orderly progress of litigation by requiring that the parties take certain procedural steps at certain specified times." *Henderson*, 562 U.S. at 435. Claim-processing rules may be "important and mandatory," but, as they do not "govern[] a

court's adjudicatory capacity," they can be waived by the parties or the court. *Id.*

The Supreme Court has adopted a "bright line" test for determining when to classify statutory restrictions as jurisdictional. *Arbaugh v. Y&H Corp.*, 546 U.S. 500, 516 (2006). A rule qualifies as jurisdictional only if "Congress has clearly stated that the rule is jurisdictional." *Sebelius v. Auburn Reg'l Med. Ctr.*, 568 U.S. 145, 153 (2013). "[A]bsent such a clear statement," the Supreme Court has cautioned, "courts should treat the restriction as nonjurisdictional in character," with the specific goal of "ward[ing] off profligate use of the term 'jurisdiction.'" *Id.* In considering whether Congress has spoken clearly, courts consider both the language of the statute and its "context, including . . . [past judicial] interpretation[s] of similar provisions." *Reed Elsevier*, 559 U.S. at 168.

"[T]hreshold requirements that claimants must complete, or exhaust, before filing a lawsuit" are typically "treated as nonjurisdictional." *Id.* at 166. Accordingly, "we have rarely found exhaustion statutes to be a jurisdictional bar." *McBride Cotton & Cattle Corp. v. Veneman*, 290 F.3d 973, 978 (9th Cir. 2002) (holding that requirement of "exhaust[ing] all administrative appeal procedures . . . before [a] person may bring an action in a court" was not jurisdictional); *see also Anderson v. Babbitt*, 230 F.3d 1158, 1162 (9th Cir. 2000) (same for provision that "[n]o decision which at the time of its rendition is subject to [administrative] appeal . . . shall be considered final so as to be agency action subject to judicial review"); *Rumbles v. Hill*, 182 F.3d 1064, 1067 (9th Cir. 1999) (same for provision that "[n]o action shall be brought . . . until such administrative remedies as are available are exhausted"),

overruled on other grounds by Booth v. Churner, 532 U.S. 731 (2001).

Section 346a(h)(1), the FFDCA's judicial review provision, provides:

> In a case of actual controversy as to the validity of any regulation issued under subsection (e)(1)(C), or any order issued under subsection (f)(1)(C) or (g)(2)(C), or any regulation that is the subject of such an order, any person who will be adversely affected by such order or regulation may obtain judicial review by filing in the United States Court of Appeals for the circuit wherein that person resides or has its principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within 60 days after publication of such order or regulation, a petition praying that the order or regulation be set aside in whole or in part.

The (g)(2)(C) order referenced above is the order "stating the action taken upon each such objection and setting forth any revision to the regulation or prior order that the Administrator has found to be warranted," which the EPA must issue at the conclusion of the administrative objections process outlined in § 346a(g)(2). *Id.* § 346a(g)(2)(C).

We must consider whether § 346a(h)(1) "clearly states" that obtaining a (g)(2)(C) order in response to administrative objections is a jurisdictional requirement. It does not. Section 346a(h)(1) "is written as a restriction on the rights of plaintiffs to bring suit, rather than as a limitation on the power of the federal courts to hear the suit." *Payne v.*

Peninsula Sch. Dist., 653 F.3d 863, 869 (9th Cir. 2011) (en banc). It delineates the process for a party to obtain judicial review, by filing suit in one of two venues within a specified time, not the adjudicatory capacity of those courts.

In *Henderson*, the Supreme Court evaluated a similarly structured provision, which provided that, "to obtain [judicial] review" of a final decision of the Board of Veterans' Appeals, "a person adversely affected . . . shall file a notice of appeal with the Court." 562 U.S. at 438. The Court found this language did "not suggest, much less provide clear evidence, that the provision was meant to carry jurisdictional consequences." *Id.* Similarly, in *Payne*, we held that an exhaustion requirement providing that "before the filing of a civil action . . . , the [administrative] procedures . . . shall be exhausted" was not a jurisdictional limit on the courts, but a requirement for plaintiffs that could be waived. 653 F.3d at 867, 869. Like the provision evaluated in *Payne*, the focus of § 346a(h)(1) on the requirements for petitioners "strongly suggests that the restriction may be enforced by defendants but that the exhaustion requirement may be waived or forfeited." *Id.* at 869.

Further, § 346a(h)(1) "does not speak in jurisdictional terms or refer in any way to the jurisdiction of the [federal] courts." *Zipes v. Trans World Airlines, Inc.*, 455 U.S. 385, 394 (1982). The word "jurisdiction" never appears. The reference to the United States Courts of Appeals "simply clarifies that, when determining in which court of competent jurisdiction they will file their claim, . . . litigants have a choice of venue." *Merritt v. Countrywide Fin. Corp.*, 759 F.3d 1023, 1038 (9th Cir. 2012) (classifying provision that an action "may be brought in any United States district court, or in any other court of competent jurisdiction" as

non-jurisdictional claim-processing rule despite its being labeled "Jurisdiction of courts; limitations on actions").

Section 346a(h)(1) similarly lacks mandatory language with "jurisdictional import." *Auburn Reg'l Med. Ctr.*, 568 U.S. at 154. It merely provides that a person "*may* obtain judicial review." 21 U.S.C. § 346a(h)(1) (emphasis added). In *Auburn Regional Medical Center*, the Supreme Court evaluated a provision with similar language, which instructed that a health care provider "may obtain a hearing" by the Provider Reimbursement Review Board if "such provider files a request for a hearing within 180 days after notice of the intermediary's final determination." 568 U.S. at 154. The Court held that the provision did "not speak in jurisdictional terms" in part because it lacked "words with jurisdictional import" like "the mandatory word 'shall.'" *Id.* Similarly, this Court has held that "permissive, non-mandatory language such as . . . . 'may file' . . . weighs considerably against a finding that [the provision] is jurisdictional." *Merritt*, 759 F.3d at 1037.

Aside from listing a (g)(2)(C) order as one of the orders available for judicial review, § 346a(h)(1) provides no indication that the administrative process required to produce a (g)(2)(C) order is a condition of the courts' jurisdiction. The objections process itself is detailed in Section 346a(g)(2), a separate provision focused entirely on administrative processes rather than on judicial review. The Supreme Court has repeatedly found that a requirement's "appear[ance] as an entirely separate provision" from the one concerning judicial review is a significant indicator of lack of Congressional intent to make that requirement jurisdictional. *Zipes*, 455 U.S. at 393–94; *see also Reed Elsevier*, 559 U.S. at 164; *Arbaugh*, 546 U.S. at 515.

The fact that (g)(2)(C) orders issued at the conclusion of administrative objections appear on § 346a(h)(1)'s list of orders for judicial review, while (d)(4)(A) orders issued in response to petitions do not, is not in itself suggestive as to whether obtaining a (g)(2)(C) order is a jurisdictional limitation. In evaluating statutes that similarly list administrative actions available for judicial review, the Supreme Court has observed that "[t]he mere fact that some acts are made reviewable should not suffice to support an implication of exclusion as to others." *Verizon Md., Inc. v. Pub. Serv. Comm'n*, 535 U.S. 635, 643 (2002). "The right to review is too important to be excluded on such slender and indeterminate evidence of legislative intent." *Abbott Labs. v. Gardner*, 387 U.S. 136, 141 (1967), *abrogated on other grounds by Califano v. Sanders*, 430 U.S. 99, 105 (1977).

The Dissent finds the language of § 346a(h)(5) suggestive of a Congressional intent to "preclude[] possible bypassing of the § 346a(g)(2) provisions." Dissent at 37. We disagree. Section 346a(h)(5) provides that "[a]ny issue as to which review is or was obtainable under this subsection shall not be the subject of judicial review under any other provision of law." This is a limitation on the availability of judicial review under *other* statutory provisions, not a pronouncement as to the internal requirements of § 346a(h)(1) jurisdiction. Similarly, *NRDC v. Johnson*, 461 F.3d 164 (2006), the Second Circuit case cited by the Dissent to support its position that § 346a(h)(5) limits this Court's jurisdiction, is inapposite. In that case, the Second Circuit held that "Section 346a(h) limits judicial review *to the courts of appeals*," rejecting an attempt by plaintiffs to challenge a tolerance by filing directly in federal *district* court under the APA, rather than filing in a federal appellate court pursuant to § 346a(h)(1). *Id.* at 173 (emphasis added). While *Johnson* also stated that § 346a(h) "forecloses such

[appellate court] review prior to the exhaustion of administrative remedies," *id.*, this was pure dictum and particularly inapposite here, since the question of whether such exhaustion was jurisdictional was not presented in that case, which expressly was concerned only with whether "decisions to leave tolerances in effect are reviewable in the district courts." *Id.* at 167.

We are also mindful what it would mean for future review of EPA decisions if we were to find obtaining a (g)(2)(C) order to be a jurisdictional requirement. In seeking to "bring some discipline" to the classification of provisions as jurisdictional, the Supreme Court has repeatedly considered how the classification of the rule in question would impact future claims. *See Auburn Reg'l Med. Ctr.*, 568 U.S. at 153–54 (examining "what it would mean" for the review process if a provision were found jurisdictional); *see also Henderson*, 562 U.S. at 434 (addressing the "considerable practical importance" that attaches to the jurisdictional label, including how jurisdictional rules "may . . . result in the waste of judicial resources and may unfairly prejudice litigants"). The impact of a jurisdictional finding must be considered within the context of the administrative process Congress was establishing in the relevant statute, and the values that process was meant to protect. For example, in *Henderson*, the Supreme Court addressed the impact of a jurisdictional finding on the process established by Congress for adjudicating veterans' benefits claims considering the "solicitude of Congress for veterans" reflected in the review scheme. *Id.*

Applying this analysis to the present case, a jurisdictional finding would mean that under no circumstances could persons obtain judicial review of a denial of a petition prior to an EPA response to an

administrative objection, even under exigent circumstances where the EPA was unwilling or unable to act. The EPA could evade judicial review simply by declining to issue a (g)(2)(c) order in response to an objection, requiring petitioners to seek writs of mandamus to order EPA action on objections. The history of this very case vividly illustrates this danger.

The language Congress used hardly suggests an intention to allow this scenario. Section 346a(g)(2) instructs the EPA to respond "as soon as practicable" to objections filed. Providing only a brief administrative review process makes sense. By the time an administrative objection is filed, the EPA has already fully considered the petition at issue and issued either a "final regulation" or, as here, "an order denying the petition." 21 U.S.C. § 346a(d)(4)(A)(iii).

Furthermore, § 346a(h)(1) provides direct access to the Courts of Appeals to challenge such EPA determinations. Broad, efficient, and prompt access to judicial review is consistent with the other values expressed by the statutory scheme: prioritizing public involvement in monitoring tolerances, as evidenced by the § 346a(d) petition process; and requiring quick EPA responses to changing scientific evidence, as evidenced by the EPA's continuing obligation to ensure that tolerances remain in compliance with the FFDCA's safety standards. *See* § 346a(b)(2)(A)(i).

We have recognized that "determining what has and what has not been exhausted . . . may prove an inexact science" and that "questions about whether administrative proceedings would be futile, or whether dismissal of a suit would be consistent with the general purposes of exhaustion, are better addressed through a fact-specific assessment of the affirmative defense than through an inquiry about whether the court has the power to decide the case at all." *Payne*,

653 F.3d at 870. Finding that a (g)(2)(C) order is a jurisdictional prerequisite would mean that courts would have no ability to analyze whether the administrative process was serving an important role in furthering the development of necessary evidence or was of little value for the issue in question, no matter the significance or the urgency of the question awaiting judicial review.

The EPA makes three main arguments that § 346a(g)(2)(C) is in fact jurisdictional. None are persuasive.

First, the EPA argues that a 1996 amendment to the language of the FFDCA's judicial review provision changing the reviewable orders listed in § 346a(h)(1), indicated a Congressional intent to condition jurisdiction over any orders not listed in Section 346a(h)(1) on their completion of the administrative appeals process. The EPA provides no support for this account of Congressional motivation, which it loosely suggests was a response to a D.C. Circuit decision from nearly a decade earlier finding that the language in the prior version did not require completing an administrative hearing process before filing for judicial review. In fact, the legislative history indicates that the amended statute "retain[ed] most of the existing provisions" regarding judicial review. H.R. Rep. No. 104-669(II), at 49 (1996). But even assuming that Congress's intent with this amendment was to have orders issued in response to petitions go through the § 346a(g)(2) administrative objections process prior to judicial review, that does not bear on the relevant question here, whether Congress intended the new rule as a claims-processing rule or a jurisdictional limitation on the courts.

Second, the EPA argues that the structure of the administrative objections process itself indicates that the process was intended as a jurisdictional requirement, rather

than a claims-processing rule. This argument relies almost entirely on the similarity between § 346a(g)(2)'s objections process and an administrative appeal process that we found jurisdictional in *Gallo Cattle Co. v. United States Department of Agriculture*, 159 F.3d 1194 (9th Cir. 1998). However, *Gallo* was premised on a view of statutory exhaustion that is inconsistent with subsequent Supreme Court precedent and later decisions in this circuit. *Compare id.* at 1197 ("[S]tatutorily-provided exhaustion requirements deprive the court of jurisdiction . . . ."), *with McBride*, 290 F.3d at 980 ("[N]ot all statutory exhaustion requirements are created equal. Only statutory exhaustion requirements containing sweeping and direct language deprive a federal court of jurisdiction."). We have specifically cautioned against reliance on prior cases like *Gallo*, "decided without the benefit of the Supreme Court's recent admonitions against profligate use of the term jurisdictional." *Merritt*, 759 F.3d at 1039. Moreover, even without this change in case law, *Gallo* would be inapposite. Unlike § 346a(h)(1), the provision evaluated in *Gallo* was explicitly jurisdictional, providing that "[t]he district courts of the United States . . . *are hereby vested with jurisdiction* to review [the administrative] ruling." *Gallo*, 159 F.3d at 1197 (emphasis added).

Finally, the EPA argues that this Court's statement in its most recent decision in the prior mandamus action forecloses this conclusion. It does not. That decision denied PANNA and the NRDC's petition for further mandamus relief because it was premised on the ground that the 2017 Order failed to meet the requirements for a final order. Rejecting that view and finding that the 2017 Order was a final denial of the 2007 Petition, this Court instructed PANNA and the NRDC that "[f]iling objections and awaiting their resolution by the EPA Administrator is a prerequisite to obtaining

judicial review of [the] EPA's final response to the petition. Only at that point may we consider the merits of [the] EPA's final agency action." *In re PANNA*, 863 F.3d at 1133. Aside from the fact that none of this language spoke to the jurisdictional issue but only to the issue of exhaustion, the instant appeal is clearly in a different posture. In compliance with our prior ruling, petitioners filed their objections, but the EPA has failed to issue a timely (g)(2)(c) order in response.

In sum, we hold that § 346a(h)(1) is not jurisdictional. It contains no jurisdictional label, is structured as a limitation on the parties rather than the courts, and only references an exhaustion process that is outlined in a separate section of the statute.

B. *Exhaustion*

Where, as here, exhaustion of administrative remedies is not jurisdictional, we "must determine whether to excuse the faulty exhaustion and reach the merits, or require the petitioner to exhaust . . . administrative remedies before proceeding in court." *Rivera v. Ashcroft*, 394 F.3d 1129, 1139 (9th Cir. 2004), *superseded by statute on other grounds as stated in Iasu v. Smith*, 511 F.3d 881, 886 (9th Cir. 2007). "In determining whether exhaustion is required, federal courts must balance the interest of the individual in retaining prompt access to a federal judicial forum against countervailing institutional interests favoring exhaustion." *McCarthy v. Madigan*, 503 U.S. 140, 146 (1992), *superseded by statute on other grounds as stated in Booth*, 532 U.S. 731.

The Supreme Court has identified the two key institutional interests favoring exhaustion as "the twin purposes of protecting administrative agency authority and

promoting judicial efficiency." *Id.* at 145. Not all cases implicate these interests to an equal degree. Exhaustion protects an agency's authority "when the action under review involves exercise of the agency's discretionary power or when the agency proceedings in question allow the agency to apply its special expertise." *Id.* Exhaustion also protects an agency's authority by providing the agency "an opportunity to correct its own mistakes with respect to the programs it administers." *Woodford v. Ngo*, 548 U.S. 81, 89 (2006). "[E]xhaustion principles apply with special force when frequent and deliberate flouting of administrative processes could weaken an agency's effectiveness by encouraging disregard of its procedures." *McCarthy*, 503 U.S. at 145.

The institutional interest in requiring exhaustion to protect agency authority appears particularly weak in the present case. The challenged action, permitting the use of chlorpyrifos on food products, does not involve exercise of the EPA's general discretion, but must take place in compliance with strict statutory directives. The questions presented in this appeal are in no way factual or procedural questions implicating the agency's "special expertise." This is not a situation, for example, where the EPA determined a pesticide was safe and the science underlying that determination is challenged. Rather, the purely legal questions here concern the statutory requirements of the FFDCA, and, accordingly, are suited to judicial determination. The crux of petitioners' challenge is that the EPA has found that chlorpyrifos is not safe and therefore cannot maintain a tolerance for it.

Allowing the petition to proceed would not reward failure to properly exhaust administrative remedies. "Proper exhaustion demands compliance with an agency's deadlines

and other critical procedural rules because no adjudicative system can function effectively without imposing some orderly structure on the course of its proceedings." *Woodford*, 548 U.S. at 90–91.

Here, petitioners timely submitted objections to the order denying the 2007 petition to revoke tolerances, fulfilling all of their exhaustion obligations except for the one not within their control—obtaining the EPA's response to the objections. Petitioners' objections were filed 13 months ago, and the key issue therein—whether the EPA was statutorily obligated to revoke the tolerance for chlorpyrifos—was first raised to the EPA over a decade ago in the 2007 Petition. This timeline has provided the EPA more than ample opportunity to correct any mistakes on its own. But, despite the statutory requirement that the EPA respond to the objections "as soon as practicable," it has failed to do so. The history of this litigation supports the inference that the EPA is engaging in yet more delay tactics to avoid our reaching the merits of the sole statutory issue raised here: whether chlorpyrifos must be banned from use on food products because the EPA has not determined that there is a "reasonable certainty" that no harm will result from its use, even under the established tolerances.

The second institutional interest identified by the Supreme Court as potentially favoring exhaustion, judicial economy, counsels against requiring further administrative exhaustion in this instance. Exhaustion offers the greatest support for judicial efficiency where it either permits the agency to "correct its own errors" such that the "judicial controversy may well be mooted, or at least piecemeal appeals may be avoided," or where administrative review "may produce a useful record for subsequent judicial consideration, especially in a complex or technical factual

context." *McCarthy*, 503 U.S. at 145. Here, it is just the opposite. Since 2012, we have issued five separate decisions related to the EPA's inaction on the chlorpyrifos tolerances. Declining to waive exhaustion at this point would make this our sixth decision on the matter without once reaching the merits, setting the stage for yet another "piecemeal appeal[]" if the EPA should someday issue a response to the petitioners' objection—something the EPA itself has strongly hinted may not come about until 2022, if then. Similarly, further development of the administrative record is of no use to judicial efficiency at this point in the proceedings; there are no factual questions, let alone "complex or technical" ones, at issue—only legal questions. And on the merits of these legal questions, the EPA offers no defense of its inaction, effectively conceding its lawlessness.

While both institutional interests favoring exhaustion are weak, this petition invokes two of the "three broad sets of circumstances in which the interests of the individual weigh heavily against requiring administrative exhaustion." *McCarthy*, 503 U.S. at 146. First, the Supreme Court has recognized that exhaustion may be excused where "requiring resort to the administrative remedy may occasion undue prejudice to subsequent assertion of a court action. Such prejudice may result, for example, from an unreasonable or indefinite timeframe for administrative action." *Id.* at 146–47. Most often, an administrative remedy is deemed inadequate "because of delay by the agency." *Id.* Here, the EPA's expressed intent to withhold action for years to come is "unreasonable" as applied here, especially as petitioners' objections concern no factual issues that would require additional time to investigate. The EPA has had over a year to respond to the objections already, with no result.

In *Coit Independence Joint Venture v. Federal Savings & Loan Insurance*, 489 U.S. 561, 586–87 (1989), the Supreme Court held that a claimant was not required to wait for a decision on its administrative appeal before seeking judicial review where the administrative appeal had been pending for over 13 months as of the date of oral argument, and there was no "clear and reasonable time limit on [the agency's] consideration of . . . claims." *See also Smith v. Ill. Bell Tel. Co.*, 270 U.S. 587, 591–92 (1926) (holding that a claimant "is not required indefinitely to await a decision of the [administrative] tribunal before applying to a federal court for equitable relief"). Like the regulation evaluated in *Coit*, the EPA's interpretation of the FFDCA's administrative review provision as providing limitless time to respond to objections would give the agency "virtually unlimited discretion to bury large claims like [petitioners'] in the administrative process, and to stay judicial proceedings for an unconscionably long period of time." *Coit*, 489 U.S. at 586. The delay is particularly prejudicial here where the continued use of chlorpyrifos is associated with severe and irreversible health effects. *See Bowen v. City of New York*, 476 U.S. 467, 483 (1986) (concluding that disability-benefit claimants "would be irreparably injured were the exhaustion requirement now enforced against them"); *Aircraft & Diesel Equip. Corp. v. Hirsch*, 331 U.S. 752, 773 (1947) (directing consideration of "irreparable injury flowing from delay incident to following the prescribed procedure" in determining whether to require exhaustion). Petitioners have been waiting over a year for EPA action on their objections, and over eleven years for an EPA decision on chlorpyrifos tolerances, while being

continually exposed to the chemical's effects. This is a sufficient basis to waive or otherwise excuse exhaustion.[2]

In light of the strong individual interests against requiring exhaustion and weak institutional interests in favor of it, we conclude that petitioners need not exhaust their administrative objections and are not precluded from raising before us the issues at hand on the merits.[3]

C. *The Merits*

We now turn to the merits. Petitioners argue that the EPA's decision in its 2017 order to maintain a tolerance for chlorpyrifos in the face of scientific evidence that its residue on food causes neurodevelopmental damage to children is flatly inconsistent with the FFDCA. Specifically, petitioners argue that a need for additional scientific research is not a valid ground for maintaining a tolerance that, after nearly two decades of studies, has not been determined safe to "a reasonable certainty," and that the EPA cannot delay a decision on tolerances to coordinate that decision with registration review under FIFRA.

The EPA presents no arguments in defense of its decision. Accordingly, the EPA has forfeited any merits-

[2] Exhaustion may also be excused where "the administrative body is shown to be biased or has otherwise predetermined the issue before it." *McCarthy*, 503 U.S. at 148. The history detailed above strongly suggests that the EPA, for whatever reason, has decided not to ban chlorpyrifos under any circumstances, even when its own internal studies show that it could not possibly make the factual findings necessary to avoid a ban.

[3] Because we find judicial review available under § 346a(h)(1), we will not address petitioners' alternative argument that judicial review is available under FIFRA, 7 U.S.C. § 136n(b).

based argument. *See Martinez v. Sessions*, 873 F.3d 655, 660 (9th Cir. 2017).

The FFDCA states unequivocally that the Administrator "shall modify or revoke a tolerance if the Administrator determines it is not safe." § 346a(b)(2)(A)(i). A tolerance is safe when "the Administrator has determined that there is a *reasonable certainty* that *no* harm will result from aggregate exposure to the pesticide, including all anticipated dietary exposures and all other exposures for which there is reliable information." § 346a(b)(2)(A)(ii) (emphasis added). Accordingly, the EPA bears a continuing obligation to revoke tolerances that it can no longer find with a "reasonable certainty" are safe.

The EPA's 2016 risk assessment concluded that its analysis of chlorpyrifos "continues to indicate that the risk from potential aggregate exposure does not meet the FFDCA safety standard" and that "expected residues of chlorpyrifos on most individual food crops exceed the 'reasonable certainty of no harm' safety standard." This finding was the EPA's final safety determination before the 2017 EPA Order. The 2017 Order declined to revoke chlorpyrifos tolerances but did not make a finding of reasonable certainty that the tolerances were safe. Instead, it found "significant uncertainty" as to the health effects of chlorpyrifos, which is at odds with a finding of "reasonable certainty" of safety under § 346a(b)(2)(A)(ii) and therefore mandates revoking the tolerance under § 346a(b)(2)(A)(i).

"[H]owever desirable it may be for [the] EPA to consult [a Scientific Advisory Board] and even to revise its conclusion in the future, that is no reason for acting against its own science findings in the meantime." *Chlorine Chemistry Council v. EPA*, 206 F.3d 1286, 1290 (D.C. Cir. 2000). The EPA cannot refuse to act "because of the

possibility of contradiction in the future by evidence unavailable at the time of action – a possibility that will *always* be present." *Id.* at 1290–91 (emphasis in original). Chlorpyrifos similarly does not meet the statutory requirement for registration under FIFRA, which incorporates the FFDCA's safety standard. As we have previously counseled, "evidence may be imperfect [and] the feasibility inquiry is formidable," but there remains no justification for the "EPA's continued failure to respond to the pressing health concerns presented by chlorpyrifos," which has now placed the agency in direct contravention of the FFDCA and FIFRA. *In re PANNA*, 840 F.3d at 105.

Accordingly, we **GRANT** the petition for review. The EPA's 2017 Order maintaining chlorpyrifos is **VACATED**, and the case is remanded to the EPA with directions to revoke all tolerances and cancel all registrations for chlorpyrifos within 60 days.

FERNANDEZ, Circuit Judge, dissenting:

League of United Latin American Citizens, Pesticide Action Network North America (PANNA), Natural Resources Defense Council (NRDC), California Rural Legal Assistance Foundation, Farmworkers Association of Florida, Farmworker Justice GreenLatinos, Labor Council for Latin American Advancement, Learning Disabilities Association of America, National Hispanic Medical Association, Pineros Y Campesinos Unidos del Noroeste, and United Farm Workers (collectively, "LULAC") petition for review of the Environmental Protection Agency's (EPA) 2017 order denying a 2007 petition to revoke all tolerances for the pesticide chlorpyrifos (hereafter "the Pesticide"). *See* Chlorpyrifos; Order Denying PANNA and NRDC's Petition

to Revoke Tolerances, 82 Fed. Reg. 16,581, 16,583 (Apr. 5, 2017) (the "2017 Order").[1] In the briefs (not in the petition for review), LULAC and the States ask for a writ of mandamus ordering EPA to respond to the objections they filed to the 2017 Order. In their brief, the States also ask for a writ of mandamus compelling the EPA to issue a final rule revoking chlorpyrifos tolerances.

The EPA regulates the use of pesticides on food pursuant to the Federal Food, Drug, and Cosmetic Act[2] (FFDCA) and the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).[3] At present, the Pesticide is registered as an insecticide for food crops and non-food settings. In the view of LULAC and the States, the Pesticide is unsafe[4] and the EPA should modify or revoke the tolerances it has established for the Pesticide pursuant to FFDCA. *See* 21 U.S.C. § 346a(a)(1)(A), (b)(1). For that matter, they believe that the EPA should cancel the Pesticide's registration for food crops under FIFRA. *See* 7 U.S.C. § 136a(g)(1)(A)(v). In September 2007, PANNA and NRDC filed an administrative petition with the EPA seeking revocation of the Pesticide's FFDCA food tolerances and cancellation of its FIFRA registrations (the 2007 Petition). On April 5, 2017, the EPA issued the 2017 Order in which it denied the 2007 Petition. *See* 82 Fed. Reg. at 16,581.

[1] The States of New York, Maryland, Vermont, Washington, California, and Hawaii, as well as the Commonwealth of Massachusetts and the District of Columbia (collectively, "the States"), are Intervenors in support of LULAC's petition.

[2] 21 U.S.C. §§ 301–399g.

[3] 7 U.S.C. §§ 136–136y.

[4] *See* 21 U.S.C. § 346a(a)(1).

LULAC and certain states filed objections to the 2017 Order on June 5, 2017, and on that same date, LULAC filed the instant petition for review of the merits of the 2017 Order.

JURISDICTION

The majority holds that we have jurisdiction over the petition for review. I disagree. Of course, we do have jurisdiction to determine whether we have jurisdiction over the petition for review. *See Special Invs. Inc. v. Aero Air Inc.*, 360 F.3d 989, 992 (9th Cir. 2004). Nonetheless, "'[w]e presume that federal courts lack jurisdiction unless the contrary appears affirmatively from the record.'" *DaimlerChrysler Corp. v. Cuno*, 547 U.S. 332, 342 n.3, 126 S. Ct. 1854, 1861 n.3, 164 L. Ed. 2d 589 (2006). Thus, "the party asserting federal jurisdiction . . . has the burden of establishing it." *Id.* Here LULAC[5] attempts to meet that burden by pointing to the judicial review provisions of FFDCA. *See* 21 U.S.C. § 346a(h).[6] It also relies on FIFRA. *See* 7 U.S.C. § 136n(b). The States also point to 5 U.S.C. §§ 704, 706 as a possible source of jurisdiction. In my view, all of those attempts fail. Hence I would dismiss the petition.

A. Jurisdiction Under FFDCA

The 2017 Order was issued pursuant to § 346a(d)(4)(A)(iii). In seeking to obtain FFDCA jurisdiction, LULAC relies upon § 346a(h)(1) which, as pertinent here, provides that:

[5] What I determine hereafter regarding LULAC also applies to the States unless otherwise indicated.

[6] Hereafter, all references to § 346a are to 21 U.S.C. § 346a.

> In a case of actual controversy as to the validity of . . . any order issued under subsection . . . (g)(2)(C) [of this section], . . . any person who will be adversely affected by such order . . . may obtain judicial review by filing in the United States Court of Appeals for the circuit wherein that person resides or has its principal place of business . . . a petition praying that the order . . . be set aside in whole or in part.

Unfortunately for LULAC's argument, the subsection referred to in the above quotation from § 346a(h)(1) is the subsection that provides for the EPA to issue an order following objections to a previous order of the EPA and that agency's processing of those objections. *See* § 346a(g)(2). That, by the way, is the process to which we pointed the parties in our earlier consideration of the EPA's proceedings regarding the Pesticide and stated that only after the review was completed "may we consider the merits of EPA's 'final agency action.'" *Nat. Res. Def. Council, Inc. v. U.S. EPA (In re PANNA)*, 863 F.3d 1131, 1133 (9th Cir. 2017). Specifically, § 346a(g)(2)(A) provides that a person may file objections to an order issued under § 346a(d)(4), as the 2017 Order was. The EPA may then hold a public evidentiary hearing upon request or upon its own initiative. *See* § 346a(g)(2)(B). An appropriate "order stating the action taken upon each such objection and setting forth any revision to the . . . prior order" must then be issued. *Id.* at (C). Pursuant to the plain reading of the above subsection taken

as a whole,[7] then, and only then, can judicial review in this court be sought pursuant to § 346a(h)(1).

But, says LULAC, the requirement is no more than a claim-processing rule[8] rather than a true jurisdictional rule.[9] The majority agrees; I am not convinced. Here Congress was very careful and very specific about the class of cases—the limited kind of orders—over which it wished to give the courts of appeals direct review. It made it plain that we could not review the EPA's actions in this specific area until the agency had developed and considered a full record regarding objections and the like. Before that occurred, judicial review was not available; we had no authority whatsoever to consider the issue. As the Second Circuit Court of Appeals has pointed out, § 346a(h)(1) is "unique in that it only commits certain specific agency actions to appellate court review." *Nat. Res. Def. Council v. Johnson*, 461 F.3d 164, 172 (2d Cir. 2006). In light of that careful restriction on judicial review, it is not at all likely that Congress would

[7] *See Nuclear Info. & Res. Serv. v. U.S. Dep't of Transp. Research & Special Programs Admin.*, 457 F.3d 956, 960 (9th Cir. 2006).

[8] *See Henderson ex rel. Henderson v. Shinseki*, 562 U.S. 428, 435, 131 S. Ct. 1197, 1203, 179 L. Ed. 2d 159 (2011) (claim-processing rules merely "seek to promote the orderly progress of litigation by requiring that the parties take certain procedural steps at certain specified times").

[9] "'Jurisdiction' refers to 'a court's adjudicatory authority.'" *Reed Elsevier, Inc. v. Muchnick*, 559 U.S. 154, 160, 130 S. Ct. 1237, 1243, 176 L. Ed. 2d 18 (2010). "Accordingly, the term 'jurisdictional' properly applies only to 'prescriptions delineating the classes of cases (subject-matter jurisdiction) . . .' implicating that authority." *Id.* at 160–61, 13 S. Ct. at 1243; *see also Payne v. Peninsula Sch. Dist.*, 653 F.3d 863, 868 (9th Cir. 2011) (en banc), *overruled on other grounds by Albino v. Baca*, 747 F.3d 1162, 1171 (9th Cir. 2014) (en banc).

have authorized our seizing jurisdiction before the specific agency action was concluded. Lest there be any doubt, Congress also precluded possible bypassing of the § 346a(g)(2) provisions when it directed that no "judicial review under any other provision of law" would be permitted. Section 346a(h)(5); *see also Johnson*, 461 F.3d at 172–74. And that is further emphasized by the fact that the section does not speak in general language of finality or exhaustion;[10] it, rather, states specifically when we can assume review authority over the particular matters. Had Congress contemplated appellate court review before the EPA completed the process required by § 346a(g)(2)(C), it could easily have inserted orders under § 346a(d)(4), or, more specifically, § 346a(d)(4)(A)(iii) into the judicial review provisions of § 346a(h)(1), which, of course, it did not do. Rather, it expressly allowed judicial review only over the agency's ruling on objections that had to be filed with the agency, and not before. *See Gallo Cattle Co. v. U.S. Dep't of Agric.*, 159 F.3d 1194, 1197–98 (9th Cir. 1998); *see also McBride Cotton & Cattle Corp. v. Veneman*, 290 F.3d 973, 979–80 (9th Cir. 2002) (discussing *Gallo Cattle*). That is particularly telling because earlier iterations of the review provisions contained no such jurisdictional limitations. *See Nat'l Coal. Against the Misuse of Pesticides v. Thomas*, 809 F.2d 875, 878–79 (D.C. Cir. 1987).

In short, I see no basis for deconstructing that carefully constructed jurisdictional scheme and thereby inviting

[10] *Cf. Anderson v. Babbitt*, 230 F.3d 1158, 1162 (9th Cir. 2000); *Rumbles v. Hill*, 182 F.3d 1064, 1067 (9th Cir. 1999).

premature attacks on matters committed to the expertise of the agency in the first instance.[11]

B. Jurisdiction under FIFRA

LULAC then argues that because it not only asked for the EPA to revoke all tolerances for the Pesticide but also asked the EPA to cancel all registrations for the Pesticide, the 2007 Petition to the EPA arose under both the FFDCA and FIFRA. Thus, it argues, it need not abide by the FFDCA review provisions, but can rely on the jurisdictional provisions of the FIFRA to establish our jurisdiction. *See* 7 U.S.C. § 136n(b). I do not agree.

Rather, I am persuaded by the cogent reasoning of the Second Circuit Court of Appeals in a strongly similar situation. *See Johnson*, 461 F.3d at 176. In that case, pursuant to the FFDCA provisions, NRDC also challenged the EPA's setting of tolerances for residues on food of five pesticides (not including the Pesticide). *Id.* at 169–70. NRDC added that their registration should be cancelled pursuant to FIFRA. *Id.* at 176. NRDC had brought its action in the district court, and on appeal the Second Circuit determined that the district court did not have jurisdiction to review the EPA determination under the FFDCA because, as § 346(a)(h)(1), (5) provide, jurisdiction over those claims was limited to the courts of appeals. *Id.* at 172–76. NRDC

[11] Because the completion of the administrative process is jurisdictional, I do not consider LULAC's fallback argument that it would be futile to pursue the prescribed process. *See Sun v. Ashcroft*, 370 F.3d 932, 941 (9th Cir. 2004); *see also Ross v. Blake*, __ U.S. __, __, 136 S. Ct. 1850, 1857, 195 L. Ed. 2d 117 (2016); *Gallo Cattle*, 159 F.3d at 1197.

then argued that the district court still had jurisdiction pursuant to FIFRA. The court replied:

> However, FIFRA's grant of jurisdiction to the district courts is irrelevant. The NRDC Appellants "challenge the registration of pesticides under FIFRA only through their challenge to the tolerances set under the [F]FDCA." Essentially, therefore, the violations of FIFRA alleged by the NRDC Appellants "amount to challenges to the methodologies used in reaching the reassessment determinations at issue" in this case. As such, these challenges represent an "issue as to which review is or was obtainable under Section 346a(h). Section 346a(h)(5) precludes judicial review of these issues "under any other provision of law." The NRDC Appellants' attempt to find independent jurisdiction for their claims under FIFRA is thus precluded by the express language of § 346a(h)(5). The NRDC Appellants' claims are reviewable only in the courts of appeals, and only after they have exhausted the statutory provisions for administrative review.

Id. at 176 (citations omitted).

I accept that reasoning and the same reasoning should apply here. It would foreclose LULAC's argument. LULAC essentially argues that the EPA has erred in maintaining tolerances for the Pesticide, which is an unsafe insecticide, and for that same reason it argues that the EPA must forthwith revoke registration of the Pesticide. It argues

that it should not have to wait for the EPA to rule on its registration claim, but that is just an allotrope of its central arguments against waiting for relief under the FFDCA tolerances provision with which its FIFRA argument is "inextricably intertwined." *See Ctr. for Biological Diversity v. U.S. EPA*, 847 F.3d 1075, 1089 (9th Cir. 2017). Therefore, the FIFRA provision does not offer a way to avoid the judicial review provisions of the FFDCA in this instance.

Thus, I would dismiss the petition for review for lack of jurisdiction.[12]

WRIT OF MANDAMUS

In its briefs, LULAC asks us to issue a writ of mandamus[13] directing that the EPA respond to its objections within sixty days. However, LULAC did not file a petition for issuance of that writ and, therefore, made no attempt to comply with the Federal Rules of Appellate Procedure when it filed its petition for review of the merits of the 2017 Order. *See* Fed. R. App. P. 21(a), (c); *see also* Fed. R. App. P. 20. I see no reason to treat LULAC's petition for review as, in fact, one for a writ of mandamus. It was not, and could not have been, a mere instance of mislabeling a request for relief that was sought. Had LULAC intended to seek a writ of

[12] I do not overlook the States' argument regarding 5 U.S.C. §§ 704, 706 (the Administrative Procedure Act provisions). But those provisions do not confer direct review jurisdiction upon this court. *See Gallo Cattle*, 159 F.3d at 1198; *see also Califano v. Sanders*, 430 U.S. 99, 106–07, 97 S. Ct. 980, 985, 51 L. Ed. 2d 192 (1977). Therefore, they add nothing of substance to the petition for review issues now before us.

[13] *See* 28 U.S.C. § 1651(a); *see also Cal. Cmtys. Against Toxics v. U.S. EPA (In re A Cmty. Voice)*, 878 F.3d 779, 783 (9th Cir. 2017).

mandamus, rather than a merits review, that would have been most peculiar because on that same day LULAC had just filed its objections to the 2017 Order. It could not honestly complain about delay in considering its objections at that point. Were I to decide otherwise, I would essentially ignore our holding, which was handed down after this petition for review was filed, but before the briefs were filed, and which declared that PANNA and NRDC must file their objections and await resolution of those objections by the EPA before we would consider the merits of the EPA's actions regarding the Pesticide. *See Nat. Res. Def. Council*, 863 F.3d at 1133.

Thus, this case is quite unlike cases where we decided that a party improperly sought to appeal an interim procedural order rather than a decision on the merits of a case, but we also considered whether we should construe the appeal as a petition for a writ of mandamus. *See Kum Tat Ltd. v. Linden Ox Pasture, LLC*, 845 F.3d 979, 983 (9th Cir. 2017) (discussing order denying arbitration request); *Johnson v. Consumerinfo.com, Inc.*, 745 F.3d 1019, 1023 & n.2 (9th Cir. 2014) (discussing order compelling arbitration and staying judicial proceedings); *see also United States v. Davis*, 953 F.2d 1482, 1497–98 (10th Cir. 1992) (dismissing request for mandamus by defense counsel in criminal conviction appeal where no petition had been filed); *EEOC v. Neches Butane Prods. Co.*, 704 F.2d 144, 146, 151–52 (5th Cir. 1983) (denying request that an appeal from a stay of proceedings pending compliance with discovery orders be treated as a mandamus petition where requesting party was represented by competent counsel and should have filed a petition therefor); *Jones & Guerrero Co., Inc. v. Sealift Pac.*, 650 F.2d 1072, 1073–74 (9th Cir. 1981) (per curiam) (refusing to construe appeal from order remanding case to

Guam Superior Court as a petition for mandamus where no mandamus petition filed).

In short, I would decline to treat LULAC's petition as one for a writ of mandamus. Of course, I express no opinion on whether or when LULAC can or should file a petition for a writ of mandamus because LULAC deems the EPA's consideration of the objections to have been unduly delayed. *See PANNA v. U.S. EPA (In re PANNA)*, 798 F.3d 809, 813 (9th Cir. 2015); *Telecomms. Research & Action Ctr. v. FCC*, 750 F.2d 70, 80 (D.C. Cir. 1984).

Thus, I respectfully dissent from parts A and B of the Discussion in the majority opinion. As a result, I do not decide the issue in part C although I do find the discussion therein does have some persuasive value.